Exhibit 5

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCT MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***This Document Relates to All Cases***	**Civil Action** No. 3:16-md-2738-MAS-RLS **MDL** No. 2738

THIRD AMENDED EXPERT REPORT OF ANNE MCTIERNAN, MD, Ph.D.

Dated: May 28, 2024

Anne McTiernan, MD, Ph.D.

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Mandate

I have been retained to review the current state of the scientific literature regarding talcum powder products and opine on whether those products cause ovarian cancer. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within. All my opinions in this report are based upon a reasonable degree of scientific and medical certainty. My time is billed at $500 per hour for the literature review and preparation of this report. A list of prior depositions and testimony is included.

Credentials, Expertise, and Experience

I am a Full Professor at the Fred Hutchinson Cancer Center in Seattle, Washington, Division of Public Health Sciences, Program in Epidemiology. I am also a Full Research Professor at the University of Washington School of Public Health, Department of Epidemiology, and the University of Washington School of Medicine, Department of Medicine, Division of Geriatrics. I am an elected member of the American College of Epidemiology, the Obesity Society, and the American College of Sports Medicine. From 2002-2012, I directed the Fred Hutchinson Cancer Center's Prevention Center.

I have received several prestigious awards for my research work including: the American College of Sports Medicine Wolffe Lecture, 2018, the American College of Sports Medicine Citation Award, 2012; the McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011; Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012; the University of Washington Roger E. Moe Award for Translational Research 2009; and the Joan P. Liman MD Award, Recipient, New York Medical College, 1989.

I received my PhD in Epidemiology in 1982 from the University of Washington, and my MD degree in 1989 from New York Medical College. I completed Internal Medicine residency training from the University of Washington in 1992. For the past 25 years, I have focused on epidemiologic research, primarily in cancer and women's health. My research studies used the methodology employed in the talcum powder products and ovarian cancer studies, namely, case-control studies, cohort studies, pooled analyses, and meta-analyses. In addition, I have had leadership positions for several randomized

controlled trials testing interventions to prevent cancer. I have published over 450 scientific manuscripts in peer-reviewed medical and scientific journals, have contributed to several academic texts, and have edited two academic texts.

I have held several leadership positions in scientific U.S. Government work. Most recently, I was a member of the 2018 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee and was a member of the 2008 U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee. I served as chair of the Cancer subcommittees for both Committees. I have served on, or chaired, grant review panels for the U.S. Department of Defense Congressionally Directed Medical Research Programs and the National Institutes of Health, and served as a program reviewer for the National Cancer Institute intramural epidemiologic research branches, for National Cancer Institute comprehensive cancer centers, and for other National Institutes of Health institutes.

I have served on editorial boards for the American Association for Cancer Research Cancer Prevention Journal, the Journal of Women's Health, and Medscape Women's Health. I have reviewed manuscripts for over a dozen prestigious journals including: Journal of the American Medical Association, Journal of the National Cancer Society, Archives of Internal Medicine, American Journal of Epidemiology, Annals of Internal Medicine, European Journal of Cancer, British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, Nutrition, and Clinical Cancer Research.

My research funding has been provided by the U.S. National Cancer Institute, the National Institutes of Health, the National Heart Lung & Blood Institute, Komen for the Cure, the Breast Cancer Research Foundation, National Cancer Institute Canada, and various pharmaceutical companies and other foundations. I have been Principal Investigator of several randomized clinical trials testing effects of various agents in relation to prevention of breast and other cancers, including exemestane, raloxifene, tamoxifen, aspirin, and vitamin D. In addition, I have been Principal Investigator of six randomized clinical trials testing effects of weight loss and exercise on biomarkers of breast and other cancers. I am co-investigator of a National Cancer Institute funded trial testing the effect of exercise on quality of life in women with ovarian cancer. I was Principal Investigator of the Seattle site of a prospective cohort study of 1100 breast cancer survivors that investigated associations of hormones, inflammation, diet,

exercise, obesity, and breast cancer survival. I was Principal Investigator of a case-control study of thyroid cancer and hormones in women, and co-investigator of a case-control study of breast cancer in men. I have published on data from other case-control studies including studies on breast cancer, pituitary tumors, melanoma, and colorectal adenomas. I have collaborated in several prospective cohort studies, resulting in lead, senior, and co-authorship of several epidemiologic manuscripts. These included the Women's Health Initiative Observational Study, the Tromso study, the Carotene and Retinol Efficacy Trial cohort, the VITAL cohort, and the Pancreatic Cancer Cohort Consortium. I have also collaborated on pooled analyses of cancer epidemiology studies.

While my major focus is in epidemiology of breast cancer, I have also published on ovarian cancer, on gynecologic cancers in general, and on women's cancers, as described below, as well as on colorectal, pancreas, melanoma, prostate, thyroid, and lung cancers. In my randomized clinical trials and prospective cohort studies, I have investigated the effects of weight loss and exercise on biomarkers of inflammation, and associations of inflammation-related biomarkers with risk of various cancers. This is highly relevant to the topic of this report, because inflammation may be one mechanism linking talcum powder products exposure and risk of ovarian cancer.

My international work in epidemiology has included work with the International Association for Research in Cancer (IARC), the World Cancer Research Fund, and the Norwegian Tromso and EBBA studies. For IARC, I chaired a working group on mechanisms for a monograph on obesity, physical activity, and cancer risk (IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1). For the World Cancer Research Fund, I was a member of the advisory panel of experts that guides interpretation of meta-analyses and systematic reviews of nutrition, physical activity, obesity, and risk for many cancers including ovarian cancer (http://wcrf.org/sites/default/files/Ovarian-Cancer-2014-Report.pdf).

From 1992 to 1997, I was the Project Director for clinical work at the Women's Health Initiative Clinical Coordinating Center. I held this role from the inception of the Women's Health Initiative, and therefore directed all aspects of development and implementation of the three clinical trials and observational study. This included development of questionnaires and protocols. Of interest to ovarian cancer and talcum powder products, one of the Women's Health Initiative questionnaires includes questions about use of talcum powder products. Furthermore, ovarian cancer was one of the primary cancers included

as an outcome in this study. As Project Director, I oversaw development of the protocol and procedures for ascertainment and adjudication of cancer outcomes, including ovarian cancer. When I stepped down as Project Director (to lead my own National Cancer Institute funded studies), I retained leadership of the outcomes work for the Women's Health Initiative through 2005. This outcomes work entailed identifying cases of specific diseases such as cancer (including ovarian), collecting medical records, and classifying cases according to standardized criteria.

Although I have not personally conducted research on talcum powder products use and risk for ovarian cancer, I have published several manuscripts on gynecologic cancers, including prevention of ovarian cancer in women at high genetic risk, as well as effects of weight and exercise on risk for ovarian cancer and on survivorship in ovarian cancer patients. In addition, I am co-investigator of a National Cancer Institute grant to test an exercise intervention on quality of life in women with ovarian cancer.

While my expertise is in the area of epidemiology, primarily in women's health and cancer research, I regularly consider the reports and studies from different scientific and medical fields including pathology, oncology, gynecology, physiology, molecular biology, and toxicology, and therefore, I have experience and expertise to consider evidence presented by experts in these fields, as I do when I prepare scientific manuscripts and grant proposals, when I review grants and manuscripts for government and private funding agencies, and when I do peer-reviewing for scientific and medical journals. Attached as Exhibit A to this report is a current copy of my curriculum vitae.

Overall Approach

The foundation for this report is based upon my education, expertise, and years of experience in designing, conducting, and interpreting epidemiologic studies, as well as my medical training. I drew upon my years of experience with synthesizing and interpreting large numbers of epidemiologic studies for comprehensive reports including work for the U.S. government, the World Health Organization International Agency for Research on Cancer (IARC), and the World Cancer Research Fund. Some descriptions of general epidemiological methods are based on descriptions in general epidemiology texts and in World Cancer Research Fund reports. (Thompson, Mitrou et al. 2018, Celentano 2019, Research Washington DC: AICR, 2007)

My opinions are based on the published epidemiologic evidence including original case-control and cohort studies, systematic reviews, meta-analyses, and pooled analyses on the topic of talcum powder products exposure and risk of ovarian cancer. In reviewing the epidemiologic literature, I used my experience as a researcher in evaluating study quality, and in determining evidence of association between talcum powder products and ovarian cancer in terms of estimated size of the effect and statistical significance. I drew upon my 41 years as a PhD-trained epidemiologist and 31 years as an MD-trained clinical scientist.

In developing my opinions in this report, I applied the same rigor and standards as I utilize in my academic and research work. In addition to my review of epidemiologic studies, I also considered and reviewed clinical, pathological, and biologic and mechanistic evidence regarding talcum powder product exposure and ovarian cancer development.

Executive Summary

This review assessed relevant published epidemiologic evidence on the association between use of talcum powder products in the genital/perineal area and risk of developing epithelial ovarian cancer. My review, as discussed more fully in this report, included 42 publications in Medline referenced scientific journals. Of these papers, 28 presented data from case-control studies (Cramer, Welch et al. 1982, Hartge, Hoover et al. 1983, Whittemore, Wu et al. 1988, Booth, Beral et al. 1989, Harlow and Weiss 1989, Chen, Wu et al. 1992, Harlow, Cramer et al. 1992, Rosenblatt, Szklo et al. 1992, Tzonou, Polychronopoulou et al. 1993, Cramer and Xu 1995, Purdie, Green et al. 1995, Shushan, Paltiel et al. 1996, Chang and Risch 1997, Cook, Kamb et al. 1997, Green, Purdie et al. 1997, Godard, Foulkes et al. 1998, Cramer, Liberman et al. 1999, Wong, Hempling et al. 1999, Ness, Grisso et al. 2000, Mills, Riordan et al. 2004, Merritt, Green et al. 2008, Moorman, Palmieri et al. 2009, Wu, Pearce et al. 2009, Rosenblatt, Weiss et al. 2011, Kurta, Moysich et al. 2012, Wu, Pearce et al. 2015, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016), 5 presented results from 3 cohort studies (Gertig, Hunter et al. 2000, Gates, Tworoger et al. 2008, Gates, Rosner et al. 2010, Houghton, Reeves et al. 2014, Gonzalez, et al 2016, O'Brien et al. 2024), 8 were meta-analyses of all epidemiologic studies up to a set date (Harlow, Cramer et al. 1992, Gross and Berg 1995, Cramer, Liberman et al. 1999, Huncharek, Geschwind et al. 2003, Langseth, Hankinson et al. 2008, Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019), one was a meta-analysis of studies with data on high-frequency genital exposure to talcum powder products and ovarian cancer risk, (Woolen, Lazar et al. 2022), one was a pooled analysis of 8 case-control studies (Terry, Karageorgi et al. 2013), one was a pooled analysis of four cohort studies, (O'Brien, Tworoger et al. 2021), one was a pooled analysis of four case-control and one cohort studies with high proportions of African-American women (Davis, Bandera et al. 2021), and one was a pooled analysis of eight case-control studies with data on history of endometriosis (Phung, Muthukumar et al. 2022). I also considered systematic reviews on talcum powder products and ovarian cancer risk, including those from the International Agency for Research on Cancer (IARC) and, later, the Canadian Government's Screening Assessment on Talc, Health Canada. (IARC is the cancer branch of the World Health Organization, an inter-governmental organization). All of these form the basis for the conclusions below. The meta-analyses, which included data summarized from all published case-control and cohort studies, consistently showed that ever use of talcum powder products in the genital/perineal area is associated with a statistically significant 22 - 31% increased risk of developing epithelial ovarian cancer overall compared with never-users. Further, the meta-analyses found a statistically significant 24

– 32% increased risk of developing serous ovarian cancer—the most common subtype of epithelial ovarian cancer—in women who had ever used talcum powder products compared with never-users. The Terry et al. pooled case-control analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall epithelial ovarian cancer and serous ovarian cancer (24%). (Terry, Karageorgi et al. 2013) The pooled cohort analysis found a statistically significant 13% increased risk of ovarian cancer in women with patent genital tracts who ever used genital talcum powder products (O'Brien, Tworoger et al. 2020); and a nonstatistically significant 8% increased risk in women overall. The most recent meta-analyses (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020, Woolen, Lazar et al. 2022), and the Terry et al. pooled case-control analysis, found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use, and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships). In addition, the Davis et al pooled analysis found that both African-American and White women were at increased ovarian cancer risk if they had genital exposure to talcum powder products (Davis, Bandera et al. 2021), and the Phung et al paper found that risk of ovarian cancer with genital exposure to talcum powder products was elevated both in women with and without histories of endometriosis. (Phung, Muthukumar et al. 2022) Phung et al. explain that endometriosis is an established risk factor for ovarian cancer. In addition, they state that endometriosis is an inflammatory disease, inflammation plays a role in ovarian cancer development, and inflammation is a possible biological mechanism for talc's association with ovarian cancer. In support of this, an analysis of Brieger et al included talc exposure in an inflammation-related risk score composed of established risk factors for ovarian cancer, and compared the score to survival in ovarian cancer patients. (Brieger, Phung et al. 2022)

Based on their systematic review, IARC classified talc-based body powder without asbestos as a 2B (possibly) carcinogen. (IARCtalc 2010) Talc with asbestos was classified as group 1 ("carcinogenic to humans"), as was talc containing asbestiform fibers. In 2021, the Health Canada screening report concluded that talc constitutes or may constitute a danger in Canada to human life or health. (HealthCanada 2021) It concluded that the current data (as of 2021) on talc and ovarian cancer are indicative of a causal effect. The Health Canada assessment was on talc itself without considering whether or not talcum powder contained asbestos.

Published laboratory and clinical studies on talc exposure and ovarian carcinogenesis have shown that in humans, talc can migrate from the perineum to the ovaries and that it can cause an inflammatory response. Elevated levels of biomarkers of inflammation (such as cytokines), as well as oxidative stress, provide biologically plausible pathways by which talcum powder product exposure can induce neoplastic transformation and result in ovarian cancer.

Given the frequency with which asbestos, a known carcinogen has been found in cosmetic and personal-use talc products, I reviewed the literature on the epidemiology of asbestos and risk of ovarian cancer. Due to the presence of not only asbestos but fibrous talc, heavy metals, and fragrance, I also reviewed literature on the carcinogenic properties of these constituents. IARC noted in its 2012 report that a causal association between exposure to asbestos and cancer of the ovary was clearly established. IARC(2012) IARC has classified asbestos and talc containing asbestiform fibers grown in an asbestiform habit as Class 1 carcinogens. IARC(2010, 2012) Talc fibers grown in an asbestiform habit are often referred to as "fibrous talc." The elongated features of fibrous talc have many of the carcinogenic properties of asbestos that are known to cause an inflammatory process. IARC(2012) contributing to the biologically plausible mechanisms to explain the carcinogenic effects of talcum powder products.

The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects of causation (Hill 1965), namely: strength, consistency across populations, temporality, biologic gradient (dose-response), plausibility, coherence, and analogy. The weight of the evidence related to genital use of talcum powder products and ovarian cancer development demonstrates a consistent increased risk. There are many instances in which relative risks less than 1.5 are widely accepted within the scientific community as being causative and have strong public health and clinical ramifications, as I point out in the report. Given the high prevalence of use of talcum powder products (as much as half of women in some studies), a relative risk/odds ratio in the range observed in these studies can have profound effects on clinical events and public health.

In my opinion, as an epidemiologist and physician, stated to a reasonable degree of medical and scientific certainty, use of talcum powder products, including Johnson & Johnson Baby Powder and Shower to Shower, in the genital/perineal area can cause ovarian cancer. I base this opinion on the statistically significant elevated risk estimates (relative risk, odds ratios) seen when the epidemiologic data are combined, the pathological evidence, the consistency of results across geographic areas and in

different race/ethnic groups, the evidence of a positive dose-response effect, and the plausible biological mechanisms.

The Science of Epidemiology

Epidemiology is the science of diseases in human populations. Epidemiologists study patterns of disease occurrence to determine causes of disease, in order to determine ways to prevent the disease from occurring. Epidemiological research studies distribution of health and disease in populations. This type of research is observational, as opposed to experimental. By relating health conditions, exposures, and behaviors to differences in the incidence of disease, associations are identified that may be causal.

In epidemiological research, an exposure is something that may influence the risk of disease. This can be something ingested such as medication, applied such as a cosmetic, breathed in, or, in the case of talc and ovarian cancer, applied to the genital area. To assess effects of exposures that have possible adverse effects with little known benefit, it would be unethical to conduct an experiment to determine effects of an exposure. For example, the effects of vitamin supplements have been tested in large-scale clinical trials to determine effects on risk for several cancers. This was considered ethical because the expectation was that the vitamin supplements could have benefit, and were unlikely to have risk, for study participants. For other exposures, however, with little expectation of benefit to offset possible adverse effects, observational studies will usually be the only available epidemiological evidence.

Much public health knowledge derives from epidemiological studies. For example, observational epidemiological studies show us that individuals who drink excessive amounts of alcohol have a high risk for developing liver failure and other diseases. Such studies have shown that persons with obesity have a high risk for developing diabetes and that smokers have high risk for developing lung cancer. Similarly, the effects of toxic agents on risk for several diseases have been identified through observational epidemiological studies. Examples include the effect of lead paint on cognitive development in children; the effect of radium exposure on bone health, blood abnormalities, and cancers; and the effect of second-hand smoke on risk for lung cancer in nonsmokers.

The associations between talcum powder product use and risk for ovarian cancer have been studied in two types of epidemiologic studies—case-control and cohort—and therefore this description of epidemiologic methodology below is limited to those types of studies.

Terminology in Epidemiological Studies

Disease incidence: The incidence of a disease is the number of new cases that occur in a population. An incidence rate is the number of new cases that occur per number of persons over an interval of time. Typically, for cancer, incidence rates per 100,000 individuals per year are determined. The incidence rate for ovarian cancer in the U.S. is approximately 11.7/100,000 women/year (https://seer.cancer.gov/statfacts/html/ovary.html).

Risk: The risk of a disease refers to likelihood of its occurrence. In epidemiological studies, risk is usually used in relative terms, that is, the risk of developing cancer in one group versus the risk in another group. In cancer epidemiology, the risk almost exclusively refers to risk of incident cancer, that is, risk of a new cancer occurrence.

Risk factor: The World Health Organization defines a risk factor as any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (http://www.who.int/topics/risk_factors/en/). Risk factors can be inherent, such as sex, age, and genetics; lifestyle-related such as diet, physical activity, or smoking; health related such as menstrual factors, reproductive history, or history of infectious diseases; toxic exposures such as minerals, metals, chemicals, or radiation; or medical, such as use of particular medications.

Exposures: In epidemiological studies, an 'exposure' is a factor or condition that may increase or decrease the risk of disease. In this report, use of talcum powder products is the 'exposure' investigated. Self-reporting of exposure could result in incomplete information. Some women may over-report use of personal products, while others may not recall whether they used the products, how often or at what quantity they used them, or for how long they continued using them. Studies in which participants are queried by trained interviewers may be able to obtain information in greater detail than when participants complete questions on a form. (Bowling 2005) However, women may be reluctant to relay sensitive personal information to an interviewer as opposed to a self-administered form. (Bowling 2005)

This type of systematic bias, however, would underestimate the relative risk, suggesting that effects of talcum powder product use in the perineal area may be stronger than reported in epidemiologic studies.

Association: Epidemiologists use the term association to describe how a disease occurrence varies as a result of the effect of an exposure. A positive association indicates that the exposure increases risk of the outcome; a negative association indicates that the exposure decreases risk of the outcome.

Etiology: The etiology is the cause or origin of a disease or condition.

Multi-factorial etiology: Very few cancers occur as a result of only one cause. Most, on the other hand, have several likely causes, each with different levels of effect. The most common risk factor for cancer is age, as older persons have increased risk for developing most of the common cancers. So, even though certain human papilloma viruses increase risk for head and neck cancers, their effect is most often seen with increasing age despite individuals acquiring the virus at a young age. For some cancers, exposures add to the effects of other exposures, or even multiply their effects. For example, both smoking and alcohol use increase risk for squamous cell carcinoma of the esophagus, but individuals who both smoke and drink have a risk of this cancer that is greater than what would be expected by adding the effects of the two exposures.

Latency period: The length of time between when a person is exposed to a causal agent and when their cancer is first diagnosed is called the latent period. This period is typically years to decades. For exposures that continue over time, it may not be possible to determine the latency period of that cancer.

Relative risk, odds ratio, and hazard ratio: The strength of a relationship between an exposure and the occurrence of disease is commonly expressed in terms of relative risk. In cohort studies, relative risk is the ratio of risk (or incidence) of a disease among people with an exposure to that among people without that exposure. In cohort studies, the hazard ratio can be used, and is the chance of an event occurring in one group (exposed) divided by the chance of the event occurring in another group (non-exposed). In case-control studies, the odds ratio is used, which is the ratio of the odds of exposure among cases to the odds of exposure among controls. Relative risks, odds ratios, and hazard ratios

above 1.0 indicate an increased risk, while those below 1.0 imply a protective effect. Therefore, a relative risk of 1.3 represents a 30% increased risk.

Statistical analyses: Epidemiologists use several types of statistical analyses to determine the size and significance of relationships among variables in sets of data. The most common in observational studies are the relative risk, odds ratio, and hazard ratio. These estimates are based on individual studies, or on pooled studies, or on meta-analyses, which are based on data from multiple studies. To determine the likelihood of these being true estimates of risk, rather than just occurring by chance, epidemiologists determine the statistical significance. For the relative risk, odds ratio, and hazard ratio, we calculate a confidence interval (CI), which shows the range of values that the true risk estimate likely represents. Most commonly, we use 95% CI, which means we are 95% sure that a true relative risk or odds ratio lies within that interval of numbers. If a confidence interval includes the number 1.0, then we say the association between the exposure and the disease could be null. Some epidemiologists consider a CI that has 1.0 at one end of the range to be of "marginal statistical significance." A similar statistic is the p-value, which estimates how likely the observed association is likely due to chance. Epidemiologists often consider a p-value less than or equal to 0.05 as "statistically significant," and often describe p-values between 0.05 and 0.09 as "marginally statistically significant." However, the term just refers to the likelihood of a chance finding.

It is important to note that "statistical significance" does not determine size of relative risk, nor does it determine whether a study provides valid and reliable information for causality. The term just refers to the likelihood of a chance finding, and should not be used to decide whether or not an exposure is causally related to disease occurrence. (Amrhein, Greenland et al. 2019) In recent years, the American Statistical Association has provided leadership on the issue of statistical testing. The association provided a statement on statistical significance and p-values, that "a p-value is the probability under a specified statistical model that a statistical summary of the data (e.g., the sample mean difference between two compared groups) would be equal to or more extreme than its observed value." (Wasserstein, Schirm et al. 2019) The statement provides several principles: 1) P-values can indicate how incompatible the data are with a specified statistical model; 2) P-values do not measure the probability that the studied hypothesis is true, or the probability that the data were produced by random chance alone; 3) Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold; 4) Proper inference requires full reporting and transparency; 5) A p-value, or statistical

significance, does not measure the size of an effect or the importance of a result; and 6) By itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis. (Wasserstein and Lazar 2016)

Both confidence intervals and p-values depend largely on the size of the population studied. If a relative risk/odds ratio indicates an effect that is consistent across studies, or that is large, we are less likely to reject the likelihood of true association, even if the confidence interval includes 1.0 or if the p-value is greater than 0.05.

Sample size: Because development of cancer can be a random event, epidemiologists strive to determine whether an association between an exposure and disease could have occurred by chance. If the study is designed appropriately, the chance of random-ness explaining observed associations is lessened. The number of cases of cancer within the study is a critical element to determining likelihood of causality.

Standardized incidence ratio and standardized mortality ratio: In some epidemiologic studies, only highly exposed persons are available for study. This is a common occurrence in studies of occupations with high levels of exposures to carcinogens, such as asbestos. Researchers typically then compare the incidence (or mortality) in the exposed cohort with the general population from which the exposed cohort is drawn. The standardized incidence ratio compares the actual versus expected number of cases of a disease, using the population data to determine expected numbers. Similarly, the standardized mortality ratio compares actual versus expected numbers of cause-specific or overall deaths. The standardized incidence ratio and standardized mortality ratio are similar to relative risks, and 95% confidence intervals are often presented.

Dose-response: “Dose response” began as a medical concept where it denotes a change in the effect of a medication or treatment according to the dose used. This concept can be applied to any exposure, including potentially toxic agents such as talcum powder products. The demonstration of a biological gradient adds weight to evidence that an exposure may be causal.

Dose response effects may be linear, where an increase in the exposure increases risk of disease at each level of increase in the exposure. A common example is the relationship between average packs/day

and years of cigarette smoking and risk for lung cancer. Alternatively, there may be a 'threshold' below which there is no effect seen, but above which there is an effect. An example is the association between exposure to menopausal hormone therapy; use for short periods has little effect on risk of breast cancer, but risk consistently increases for five years' or longer use.

Alternatively, the effect may be to influence risk one way at both low and high levels of exposure, but the other way at intermediate levels of exposure, shown as 'J'- or 'U'-shaped curves. In such cases, the exposure is evidently beneficial or harmful only within certain ranges. For example, intake of alcohol at small amounts has been related in some studies to lower risk of cardiovascular disease, whereas heavy intake increases risk.

Some exposures that are continuous variables are often reported in discrete categories. Although this is done for statistical reasons and can make effects easier to detect, the number and location of category boundaries may obscure the true relationship between exposure and the outcome, and non-linear effects of exposure may be missed if inappropriate categories are used.

Bias: A systematic error in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure and the outcome.

Confounding: This type of bias occurs when a third variable interferes with a true relationship between an exposure and an outcome. A confounding variable is one that is related to the risk of disease and to the exposure. It is not by itself a cause of the disease and does not lie in the pathway between the exposure and disease. The epidemiologic studies reviewed for this report all adjusted for potential confounding factors.

Effect modification: In some persons, an exposure increases risk of disease while in others it has no effect or has a smaller effect. This is called effect modification. An example is that obesity has a larger effect on risk for colon cancer in men than in women.

Generalizability: The goal for epidemiologic research is to identify causes of disease that can be applicable to all populations. Most modern-day case-control studies attempt to do this by conducting population-based studies. That is, they identify all cases of a cancer occurring in a population and

attempt to interview as many of those cases as possible. They also identify a similar sample of persons from the same population who do not have cancer and attempt to interview as many of those as possible. Many of the case-control studies of talcum powder products identified cases through population-based cancer registries, which register almost 100% of cases of cancer occurring in the population served by the registry. These population-based studies are better able to produce results that are generalizable to the whole population. Hospital-based case-control studies of ovarian cancer include all cases of the cancer that present to a hospital and compare them to a comparable group of hospitalized patients without cancer. While the comparisons between cases and controls can be valid, the generalizability of the results to the population can be low if patients from the recruiting hospital differ from the population as a whole.

Generalizability can be more of an issue for cohort studies, depending on how the study participants were recruited. Three cohort studies have reported on talcum powder product use and ovarian cancer risk. The Women's Health Initiative recruited from the general population of postmenopausal women from 40 clinical centers around the U.S. The rate of response was only around 1-2%, however, and therefore the cohort is unlikely to represent the population of American postmenopausal women. The Nurses' Health Study recruited nurses from around the U.S. Their rate of response was higher than for the Women's Health Initiative, but they are all nurses, and therefore have different health knowledge, income, and socioeconomic status compared with the general U.S. population. The Sister Study recruited from the general population, targeting women who had at least one sister with breast cancer. The responding participants therefore represent only women with a family history of breast cancer, and given their self-selection, likely differ from the general population in vulnerability to cancer and other characteristics.

Exposure measurement: Defining whether a person is exposed to a potentially causal agent is critical to the science of epidemiology. For many exposures, we must rely on what the individual can tell us about their health habits, lifestyle, work history, and use of products and medications. Recall of these variables can be challenging. Epidemiologists, therefore, often have interviewers use tools to jog participants' memories, such as anchoring around particular ages and life events. The most thorough case-control studies queried about both frequency and duration of use of talcum powder products, as well as brand and type of product, and areas of exposure (e.g., perineal, sanitary napkin, other body areas, diaphragm, etc.) The ascertainment of use of talcum powder products is difficult, especially in determining dose of

exposure, because women may have been using powders without being aware of what the product contained. Furthermore, information on the variable contents of talcum powder products (talc, fibrous talc, asbestos, other metals, fragrance) was not available to the scientists conducting the epidemiologic studies. While many epidemiologic case-control studies of talcum powder products and ovarian cancer risk asked women for brand names and dates of use, and analyzed data separately by likely powder contents, these analyses will not have been able to identify the various constituents of talcum powder products.

The Women's Health Initiative asked women about duration of use of talcum powder products but did not ask about frequency of use. (Houghton, Reeves et al. 2014) The Nurses' Health Study asked about frequency of use but did not query regarding duration of use. (Gertig, Hunter et al. 2000) The Nurses' Health II study (part of the cohort pooled analysis) asked about duration of use but not frequency of use. (O'Brien, Tworoger et al. 2020) The Sister Study asked participants about use and frequency of talcum powder products in the 12 months before study enrollment (and age 10-13). (Gonzalez, O'Brien et al. 2016) None of the cohorts, therefore was able to estimate total lifetime dose of talcum powder product exposure.

Issues in talcum powder product exposure measurement are shown clearly in a new publication of genital talc exposure patterns in the Sister Study "Douching and Genital Talc Use: Patterns of Use and Reliability of Self-Reported Exposure". (O'Brien, Ogunsina et al. 2023) This study collected additional data during follow-up from a subset of 36,202 women in the Sister Study cohort. Cohort women had been asked to report use of talc in the genital area in the year before study entry and at ages 10-13. In the follow-up data collection, women were asked about their use of talc in the genital area over their lifetimes. They were asked whether they ever used talc in the genital area, how old they were when they first used the product and when they last used the product, with an option to indicate current use. Women were then asked about use of talc in genital areas during each decade of life, including frequency of use (1 per year or less, 2-11 times per year, 1-3 times per month, or once a week or more). When analyzing these data and comparing to the original Sister Study questions on year-before-study-entry data, 87% of responses about genital talc exposure agreed. This represents a very high level of agreement and shows that women report talc exposure to genital areas with high reliability.

However, this paper also points out the amount of under-reported genital talc exposure if a study fails to ask about lifetime exposure. The original Sister Study reported on associations between women's genital talc use in the year before entering the cohort (2003-2009) and development of ovarian cancer. (O'Brien, Tworoger et al. 2020) Of the 41,500 women in the cohort, only 14% reported ever using talc in the genital area during that one year. In contrast, the Sister Study patterns of use survey asked about lifetime use of talc in the genital area, to which 32% of women reported ever having used talc in the genital area. This shows the greater than 2-fold under-reporting of talc exposure in the genital area in the original Sister study that asked only about talc use in the year before study entry. For the pooled cohort study, the Sister Study genital talc exposure was calculated from both the year-before-study entry data and the exposure at ages 10-13 years, and a reported 27% of women had every used talc in the genital area. (O'Brien, Tworoger et al. 2021) Note this 27% is still less than the 32% reported by the Sister Study patterns of use survey. This level of under-reporting of talc exposure to genital areas shows considerable misclassification of exposure.

Under-reporting (or over-reporting) of exposures, a type of misclassification, will underestimate a true relative risk if the misclassification does not depend on whether it occurred in cases or non-cases. (Flegal, Brownie et al. 1986) Therefore, the estimated relative risks in studies that looked at effects of talcum powder product use and risk of ovarian cancer are likely to be under-estimates of true relative risks. This is important for both cohort and case-control studies, but will especially affect cohort studies since they either have data only from a short period of time (e.g. one year in Sister Study) (Gonzalez, O'Brien et al. 2016) or do not update exposure after baseline data collection (e.g. Women's Health Initiative, Nurses' Health Studies, Sister Study). (Gertig, Hunter et al. 2000, Houghton, Reeves et al. 2014, Gonzalez, O'Brien et al. 2016)

Diagnosis and classification of disease outcome: "Outcome" refer to the disease or health condition of interest; in this report, any type of epithelial ovarian cancer is the outcome. In some reports, cancers of the fallopian tubes and peritoneum are combined with epithelial ovarian cancer, as they are believed to be the same biological process and are treated the same as ovarian cancer with surgery and chemotherapy (https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq).

Determination of outcomes (sometimes called "events") is a critical part of epidemiologic research. If cases of a disease are over- or under-counted, results of exposure-disease associations will be skewed. If

the source of cases differs from the source of controls, comparisons between cases and controls may be biased. In case-control studies, researchers try to include all cases that were newly diagnosed with the disease in a defined population within a set period. Population-based cancer studies often identify cases through population-based cancer registries. Hospital-based studies, conversely, identify cases that were newly diagnosed in one or more hospitals. Whichever method is used, researchers try to include and interview as high a proportion as possible of identified cases, to reduce chances of biased results.

For epidemiologic studies of cancer, it is important to identify, at the minimum, the type of cancer, stage of cancer at diagnosis, and subtype of cancer. Using pathologists' reports from medical records, trained coders classify patients into the correct categories depending on the pathology and other medical records. There are several different subtypes of cancer of the ovary. Over 90% originate in epithelial tissues and are called "epithelial ovarian cancers." The remaining 10% originate in other ovarian tissues (germ cell or sex-cord stromal). Of the epithelial ovarian cancers, approximately 70% are serous, 10% are endometrioid, 12% are clear cell, 3% are mucinous, 1% are Malignant Brenner, and the remaining are mixed histologies. (Rojas, Hirshfield et al. 2016) Epithelial ovarian cancer may be invasive or borderline. Only epithelial ovarian cancer has been studied in relation to use of talcum powder products. Therefore, in this report, "ovarian cancer" refers to "epithelial ovarian cancer."

Types of Epidemiologic Studies on Ovarian Cancer and Exposure to Talcum Powder Products

Epidemiologists have assessed the relationships between use of talcum powder products and risk of ovarian cancer development, using several types of epidemiologic studies. The studies with the greatest number of cases of ovarian cancer used case-control designs. Most of these were designed specifically to address use of talcum powder products as a potential cause of ovarian cancer. Three cohort studies have also reported on associations between talcum powder product use and risk of ovarian cancer. These cohort studies were designed to test hypotheses relating hundreds of exposures to scores of disease outcomes including common cancers, cardiovascular disease, cerebrovascular disease, musculoskeletal diseases, and others. Finally, after several epidemiologic studies were published, researchers combined data from these studies using either meta-analyses or pooled analyses. The pooled analysis also included data from previously unpublished studies, and therefore provide

additional information beyond just summarizing results of published studies. All of these studies contribute to the science of the epidemiologic evidence relating use of talcum powder products to risk of ovarian cancer development. The totality of evidence on the causal effect of talcum powder product use on ovarian cancer development relies on data from epidemiologic studies, pathological evidence of migration to the ovaries of talc and other constituents of talcum powder products (such as asbestos), and laboratory evidence.

Critical Components to Both Case-control and Cohort Studies

1) The accurate and complete ascertainment of cases. In case-control studies, this means that all cases of ovarian cancer should be identified in a given population and as high percent of them should be included in the study as possible. The controls should be free of ovarian cancer and should be as similar as possible to the cases except for the exposure under study. In cohort studies, this means that all individuals should be followed over time to determine how many did or did not develop ovarian cancer. For both types of studies, cases should be confirmed by medical record and pathological report review.

2) Precise determination of exposure. In both case-control and cohort studies, both cases and non-cases should have completed questionnaires about their current and past history of use of talcum powder products, including how often they used the products, when they began use, and number of years used. In case-control studies, this is often done with the help of a trained interviewer. In cohort studies, which typically involve larger numbers of participants because only a small fraction will go on to develop specific diseases, questionnaires are usually self-administered without the assistance of an interviewer. In cohort studies, exposures should be updated after the baseline assessments, to ensure that changes in exposure can be captured. For an exposure like talcum powder product use, lifetime use would be relevant for determining total exposure. For both case-control and cohort studies, determining early life exposures depend on participants' ability to recall typical use patterns. Interviewer-administered surveys would typically include prompts to help participants recall past habits. Self-administered questionnaires may include some printed prompts, but these are usually minimal.

For a rare endpoint like ovarian cancer, a cohort must be followed for decades in order for a sufficient number of cases to accrue to determine effects of particular exposures. Therefore, there is the possibility of bias towards the null via changes in behavior over the course of the decades of follow-up.

A woman who was originally classified as an "ever" talc user will remain an "ever" user even if she subsequently discontinued talc use. A "never" user who subsequently begins talc use will always be misclassified as a never user unless a follow-up survey records her change in status.
In ideal situations, the precise nature of the exposure would be verified. Despite habitual use, however, quantification of exposure is difficult.

(3) For both case-control and cohort studies, the populations should be well-characterized, so that any potential confounding variables can be accounted for in comparing exposure rates of cases and non-cases.

Case-control Studies

In case-control studies, individuals diagnosed with a specific type of cancer (cases) are compared with otherwise similar individuals who have not been diagnosed with cancer (controls). The control group is a sample of the population from which the cases arose and provides an estimate of how the exposures being studied are distributed in that population. In the ideal case, the controls will be similar to the cases on all variables other than the exposure under question. Therefore, epidemiologists often match controls to cases on such variables as age, race, and ethnicity, or they include a large enough sample of participants that they can adjust for these variables.

Case-control studies can enroll a large number of cases, are usually less expensive than cohort studies, and can be completed over shorter periods of time. Relevant to this report, case-control studies also can be designed to answer specific questions related to one outcome, and participants can be queried in detail about certain exposures. Selection bias is an increasing problem if participation rates among case and control groups is substantially less than 100 percent, and where participation may be related (in different ways) to various exposures.

Case-control studies are subject to their own limitations, including recall bias, which can occur when participants' reports of various exposures are differentially affected by whether they are cases or controls in the study. This is a theoretical bias however; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls. (Coughlin 1990)

One of the case-control studies of talcum powder product use and ovarian cancer risk (Schildkraut, Abbott et al. 2016) addressed this issue by counting as "users" only women who had used talcum powder products for at least six months, on at least a monthly basis. This procedure minimizes the potential over-reporting of minimal exposure by cases versus controls.

For this report, I reviewed 28 case-control studies, for most of which the association between use of talcum powder products and risk of ovarian cancer was a primary research questions.

Cohort Studies

In prospective cohort studies (usually called cohort studies), the exposures of a large group (cohort) of people who are assumed to be healthy are assessed, and the group is followed over a period of time. During the follow-up period, some members of the cohort will be diagnosed with cancer, while others will not, and comparisons are then made between these two groups. Cohort studies may need to be very large (up to hundreds of thousands of participants) to have sufficient statistical power to identify factors that may increase cancer risk by on the order of 20 or 30 percent. In addition, meaningful comparisons between cases and non-cases can be made only for factors that vary sufficiently within the cohort. Importantly, cohort studies must identify exposures of interest when participants are enrolled into the study, in order to determine effect of the exposures on eventual development of the outcome of interest. Alternatively, if an exposure is ascertained some time after enrollment (as in the Nurses' Health Study ascertainment of talcum powder product use), the researchers will consider the date of collection of that exposure data to be the start date for follow-up of study participants. Because cohort studies typically are designed to look at multiple outcomes such as cancers, cardiovascular diseases, mortality, and other diseases, information collected on exposures tends to be minimal, to pertain to current levels of exposure, and may not be updated during follow-up.

Cohort studies provide the opportunity to obtain repeated assessments of participants' exposures at regular intervals, which may improve the assessment of the exposures. However, for this to happen, the investigators need to have planned for repeated measures of the exposure. In published cohort studies of talcum powder products and ovarian cancer risk, no repeated measures of talcum powder products were reported.

In cohort studies, the ascertainment and adjudication of cancer outcomes can be accomplished by directly asking participants about illnesses and hospitalizations, and requesting medical records for reviewing these events. In some cases, ascertainment of disease events may be accomplished by linking to a cancer registry.

For this report, I reviewed results of 3 cohort studies, published in 5 papers. None were designed specifically to look at the association between talcum powder product use and risk of ovarian cancer. Further, none of these studies fully ascertained exposure to talc, as will be discussed below.

Meta-analyses and Pooled Analyses

Because there can be random variations within individual epidemiologic studies, and because very large sample sizes may be needed to see effects on rare diseases, epidemiologists rarely make causal inferences based on results of one study. Rather, we look at the totality of epidemiologic studies to determine patterns of exposure-disease relationships. Meta-analysis is a method used to combine the statistical results of several studies to produce an average estimate of effect of an exposure on an outcome of interest. These summary estimates can provide evidence regarding the presence or absence of an association and can allow examination of dose-response relationships. In the area of talcum powder products use and ovarian cancer, 8 comprehensive meta-analyses have been published on studies up to dates of publications (Harlow, Cramer et al. 1992, Gross and Berg 1995, Cramer, Liberman et al. 1999, Huncharek, Geschwind et al. 2003, Langseth, Hankinson et al. 2008, Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019), three of which are more recent and covered all studies contained in the previous meta-analyses. (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019) The Woolen et al. meta-analysis (Woolen, Lazar et al. 2022) focused on high-frequency use of talcum powder products, which was not available for all studies.

In pooled analyses, original individual-level data from various published and/or unpublished epidemiological studies are combined and re-analyzed. The combination of data from multiple studies creates a larger data set and increased statistical power. One earlier pooled analysis was published on the relationship between talcum powder product use and risk of ovarian cancer, and is heavily cited in

this report because of its significance in including very high numbers of women with ovarian cancer and controls, thereby providing a high degree of statistical power. (Terry, Karageorgi et al. 2013) Two additional pooled analyses were published more recently, that focused on subgroups of women: 1) African-American women (Davis, Bandera et al. 2021) and 2) women with and without a history of endometriosis. (Phung, Muthukumar et al. 2022)

The meta-analyses that I reviewed for this report included data from available cohort and case-control studies. I also reviewed the pooled analysis of 8 case-control studies (Terry, Karageorgi et al. 2013), the pooled analysis of cohort studies (O'Brien, Tworoger et al. 2020), and the pooled analyses by Davis et al. and Phung et al. (Davis, Bandera et al. 2021, Phung, Muthukumar et al. 2022) In addition to effect measures (relative risks, odds ratios, hazard ratios) and their confidence intervals (or other test of statistical significance such as p-value), I reviewed the number of people with and without disease for each exposure category, method of exposure ascertainment, estimated exposure categories, assessment of dose-response effects, and effect sizes for all epithelial ovarian cancer and for subtypes of epithelial ovarian cancer (invasive, borderline, serous, endometrioid, mucinous, clear cell).

Possible Sources of Bias in Epidemiologic Studies Reviewed

All studies of all types must be critically evaluated for both strengths and potential limitations in order to determine the totality of evidence. Limitations in epidemiologic studies are often characterized as biases. These include the biases listed below. It is important to note that the presence of bias does not render an epidemiologic study invalid. Rather, biases are issues that should be carefully considered when assessing how much weight should be given to individual studies, and what conclusions can be drawn from them.

Missing data: Both case-control and cohort studies can suffer from missing data. If the missing data items are related to the use of talcum powder products, then the estimated relative risks/odds ratios will likely be artificially low. If, in cohort studies, the cases of ovarian cancer are not identified, i.e., the cancer data are missing, the statistical power to detect statistically significant effects will be lessened. Both of these conditions would likely mean the true association between use of talcum powder products and risk of ovarian cancer is actually higher than what is observed in the epidemiologic studies.

Poor precision of exposure measurement: Determining whether, how much, and for how long women were exposed to talcum powder products is difficult. Women may not remember the brand of powder products they used, and contents of personal powder products may not be clear or may change over time. Women may not remember the amount of products used, frequency of use, and years of use. The underestimation of talcum powder product exposure to the genitals will result in bias to the null. (Copeland, Checkoway et al. 1977) If a study collects information in such a way that exposure is overestimated regardless in both cases and non-cases, that will also drive the relative risk toward the null value. (Copeland, Checkoway et al. 1977). This type of nondifferential misclassification, i.e., underestimating (or overestimating) exposure to talcum powder product, biases the relative risk toward the null value. That is, it would likely underestimate the relative risk, suggesting that true effects of talcum powder product exposure is stronger than reported in epidemiologic studies.

Publication bias: The publication of epidemiologic studies depends on several factors. The investigators must have developed hypotheses about certain questions and designed the study accordingly, including asking the correct questions about the exposure and potential confounding variables, and collecting information from a sufficient number of participants. The investigators then need to perform statistical analyses, develop scientific manuscripts, and submit for journal publication. It may be difficult to find a journal that will accept null results (i.e. where an exposure is shown to not be related to an outcome). (Rising, Bacchetti et al. 2008, Sridharan and Greenland 2009) The pooled analysis of case-control studies provides some reassurance that publication bias is less likely for this association. (Terry, Karageorgi et al. 2013) Of the 8 studies included in that analysis, 3 had not been previously published. Ever use of talcum powder products in the genital area produced odds ratios of 1.37 (95% CI 1.07–1.67), 1.36 (95% CI (1.06–1.74), and 0.99 (95% CI 0.70–1.41) for the 3 individual studies. That the confidence intervals overlapped, and that 2 of the 3 studies showed statistically significant associations, suggest low publication bias for the association between use of talcum powder products in the genital area and risk of developing ovarian cancer.

Cancer process affecting likelihood of exposure: If women used talcum powder products in the perineal area due to symptoms from an early cancer process, results of studies could be biased. Cohort studies often guard against this by eliminating cases that develop within a short time of study enrollment. Case-

control studies guard against this by asking participants to recall exposures one or more years prior to their cancer diagnosis (and similarly ask controls to recall exposures at least one year prior to interview).

Confounding: Variables related to both use of talcum powder products and risk of ovarian cancer could mask the true relationship between these variables. Epidemiologists handle this by adjusting in the analysis for these potential confounding variables. All of the studies reviewed performed adjustment for several potential confounding variables. Those studies that presented both adjusted and unadjusted odds ratios/relative risks found little effect of confounding variables on these relationships.

Recall bias: For the case-control studies, media reports of associations between talc and ovarian cancer could have influenced cases such that they recalled use of talcum powder products to a greater degree than controls. However, the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward. Thus, "recall bias" is unlikely to be an issue. As mentioned above, recall bias is a theoretical bias; studies that have investigated other sources of data on exposures have failed to confirm the presence of differential recall between cases and controls. (Coughlin 1990)

Non-response bias: Case-control studies with low levels of response in cases or controls can be biased, in that the non-responding cases and controls could differ with respect to use of talcum powder products.

Differential results of cohort versus case-control studies: Ideally, results of case-control and cohort studies would be similar for the relationship between an exposure and risk of disease. However, there could be several reasons for discrepancy in results between case-control and cohort studies. The exposure measurement may differ in the two types of studies. For example, cohort studies may measure exposure at study entry without updating and without ascertaining lifetime exposure. The study would then have only one time point of an exposure that could significantly attenuate the observed associations between exposure and disease.

Population-based case-control versus hospital-based case-control studies: For some exposure-disease relationships, population-based case control studies are the most valid method of comparing risk for exposed versus non-exposed persons because the risks to public health can better be estimated. For

others, however, hospital-based case control studies may provide important information because controls with illnesses may be more likely to recall exposures compared with healthy controls from the community, and therefore recall bias can be reduced.

Causal Inference in Epidemiology

The overarching goal of epidemiologic research is to determine likely causes of disease, in order to determine who is at risk for that disease and how to prevent the disease in individuals and populations. Much of epidemiologic observational research in cancer focuses on determining the *associations* between an exposure and an outcome. In other words, in a sample of individuals, are the number of persons exposed to an agent more likely to develop a cancer than those who are not exposed? There are several related questions. For example, will the persons who are exposed to a higher dose have an even greater risk than persons with little exposure? Will those exposed for a longer period of time have greater risk than those exposed for only a short time? Epidemiologists follow guidelines and logic in determining likelihood of an exposure causing cancer. (Rothman and Greenland 2005) In addition to epidemiologic data, epidemiologists also consider plausible biological mechanisms to explain observed associations. The weight of evidence depends on the validity of the data as well as the clinical and biological evidence, if available, to explain these associations.

In epidemiology, and therefore in this report, a positive association means that the exposure in question increases risk for a disease or outcome. A negative association refers to an exposure decreasing risk for the outcome.

In 1965, English epidemiologist Sir Austin Bradford Hill attempted to describe several aspects of the causal relationship in a speech to the Royal Society of Medicine's newly-established Section of Occupational Medicine. (Hill 1965) As Bradford Hill explained, this is not a checklist of factors to be counted: "What I do not believe—and this has been suggested—is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*."

These aspects of a causal relationship are:

Strength of the association. If the risk of developing cancer is several times higher in persons exposed to a toxic agent, that increases the likelihood of causality. It is not a necessary condition for establishing causality and providing recommendations for avoiding a potential cancer-causing agent, however. Indeed, several known carcinogens raise risk of cancer to less than doubling of risk. As Bradford Hill pointed out in his address: "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so."(Hill 1965)

Several examples follow:

Alcohol and risk for postmenopausal breast cancer: Risk for postmenopausal breast cancer increases by approximately 10% (a relative risk of 1.1) for each 10 gram/day intake of alcohol (the amount in a four-ounce glass of wine). (Thompson, Mitrou et al. 2018) Women are advised to avoid alcohol or minimize alcohol intake to no more than one alcoholic drink per day to reduce risk for this cancer. (Thompson, Mitrou et al. 2018)

Air pollution and risk for cardiovascular disease: A 2013 meta- analysis found that for each 10 µg/m3 rise in $PM_{2.5}$, the air pollution caused by motor vehicles, yields an 15% increase in risk of cardiovascular disease (similar to a relative risk of 1.15). Given the widespread prevalence of exposure to ambient pollution, even modest contributions to cardiovascular disease risk can have a substantial effect on population health. (Cosselman, Navas-Acien et al. 2015)

Outdoor particulate matter air pollution and lung cancer: A 2014 meta-analysis including 18 studies showed a relative risk of 1.09 (95% CI 1.04-1.14) per 10-µg/m^3 of exposure to particulate matter ($PM_{2.5}$). (Hamra, Guha et al. 2014) This is highly significant, because 10-µg/m^3 of exposure to $PM_{2.5}$ is the lowest recommended limit set by IARC for minimizing health effects of air pollution.

Benzene at work and risk of leukemia: In 2010, a meta-analysis of 15 epidemiologic studies found that worksite benzene exposure increased risk of any leukemia by 40% (relative risk 1.40, 95% CI 1.23-1.57). (Khalade, Jaakkola et al. 2010)

Estrogen-progestin menopausal hormone therapy and breast cancer risk: The Women's Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke). (Rossouw, Anderson et al. 2002) A meta-analysis of clinical trials and observational studies in 2018 found that use of this therapy increased risk of breast cancer by 59% (relative risk 1.59, 95% CI 1.40-1.81). (Kim, Ko et al. 2018) These results led to FDA-required label warnings on estrogen and progesterone therapy preparations (Key, Appleby et al. 2003), and to clinical warnings against use of estrogen plus progesterone for prevention of chronic conditions. (Grossman, Curry et al. 2017)

Trichloroethylene and risk of kidney cancer: In 2012, a meta-analysis was published showing that occupational exposure to trichloroethylene was associated with an approximately 30% increased risk for kidney cancer (relative risk 1.32, 95% CI 1.17-1.50). (Karami, Lan et al. 2012)

Regular physical activity is associated with reduced risk for cardiovascular disease, diabetes, and various cancers in persons who meet national physical activity guidelines of 150 minutes/week of moderate-intensity aerobic activity. (U.S. Physical Activity Guidelines Advisory Committee 2018 report) (2018) In one large pooled analysis of 6 cohorts with 661,137 men and women, investigators found a 20% lower mortality risk among those performing less than the recommended minimum of 7.5 metabolic-equivalent hours per week (hazard ratio, 0.80 [95% CI, 0.78-0.82]), a 31% lower risk at 1 to 2 times the recommended minimum (hazard ratio, 0.69 [95% CI, 0.67-0.70]), and a 37% lower risk at 2 to 3 times the minimum (hazard ratio, 0.63 [95% CI, 0.62-0.65]). (Arem, Moore et al. 2015) To compare with the relative risks for adverse exposure, one would look at the inverse of the hazard ratios, i.e., 1.25, 1.45, and 1.59.

Intermittent intense sun exposure and risk of melanoma: A 2005 meta-analysis included data from 57 epidemiologic studies with 38,671 cases of melanoma, and found a relative risk of 1.61 (95% CI 1.31-1.99) for intermittent intense sun exposure. (Gandini, Sera et al. 2005)

Prevention of skin cancer with use of sunscreen has also been observed, with similar effect sizes. In a 4.5-year trial with an additional 8-years follow-up, individuals randomly assigned to daily sunscreen use had almost a 40% reduced risk of squamous cell carcinoma (rate ratio, 0.62; 95% confidence interval, 0.38-0.99). (van der Pols, Williams et al. 2006) To compare with the relative risks for adverse exposure, one would look at the inverse of the risk ratio, i.e., 1.6.

It is critical to note that there are no standardized definitions of what relative risk (or odds ratio or hazard ratio) that defines "weak," "moderate," or "strong" associations. These are subjective categories, and the use of these or similar words varies among authors. For a cosmetic product, the observed increased relative risks of ovarian cancer, a life-threatening disease, seen in the epidemiologic studies is not an acceptable risk, and should not be characterized as "weak" or "small."

Consistency of the association. A consistent association would be observed in various populations, places, circumstances, and times. Has the association been found in different countries, in persons from various race/ethnic groups, and of different ages? This is also not a requirement, as there could be occasions when an exposure only increases risk for specific categories of individuals. An example, again from the breast cancer field, is that obesity increases risk for breast cancer occurring after menopause but decreases it for women who have not yet undergone menopause. Relevant to the association between ovarian cancer risk and use of talcum powder products, the association has been observed in the U.S., Canada, China, Australia, Israel, and the UK. While most data have been collected in Whites, a positive association between use of talcum powder products and risk for ovarian cancer has also been found in Blacks and Asians.

Specificity of the association: This suggests that if an exposure causes only one type of disease, that its causal link to that disease is strengthened. However, Bradford Hill recognized the limits of this aspect. One noxious agent, such as tobacco smoke, is an accepted cause of multiple cancers as well as cardiovascular disease. Similarly, one disease can have multiple causes. For example, lung cancer risk is increased with exposure to radon and asbestos, even in persons who do not smoke. In support of this, Bradford Hill stated, "One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation…"(Hill 1965)

Temporality: The time course between exposure and disease occurrence is an important consideration. Bradford Hill was referring to the need to document that the exposure came before the disease, rather than something about the disease causing a person to come into contact with the exposure. This is why, for case-control studies, researchers have often queried women about their lifetime history of use of talcum powder products, beginning from young ages. Some cohort studies, on the other hand, asked about current use of these products when the women were first enrolled in the cohort. However, for all of these studies, only talcum powder product use prior to the cases' diagnoses (and prior to a comparable time point for controls, in case-control studies) was counted as "exposure."

Biologic gradient*:* This refers to the dose-response curve or the shape of the association between exposure and risk as the amount of exposure changes. If risk for a disease increases with increasing amount of exposure, the likelihood of a causal relationship is often increased. The exposure can be classified by total duration of exposure, by usual amount of exposure, or by a combination of these two. For use of talcum powder products, dose has been estimated by total years of use, by frequency of use, and by a combination of these two variables. It should be noted that ovarian talc particle burden may not be influenced by number of applications of perineal talc usage (Heller, Westhoff et al. 1996), and therefore the typical dose-response relationship may not be necessary for establishing causality between perineal talcum powder product use and risk for ovarian cancer. Indeed, there are numerous substances, such as asbestos, for which there is no safe dose.

Plausibility: The association is strengthened if it is biologically plausible. However, Bradford Hill recognized that "What is biologically plausible depends upon the biological knowledge of the day." It is important to note that biologic plausibility does not require proof of mechanism.

Coherence: The cause-and-effect interpretation of the data should not significantly conflict with the known facts about the natural history and biology of the disease. Therefore, for example, the concurrent rise in tobacco smoking rates and rise in lung cancer incidence in the 20th century in the U.S., as well as the more recent concurrent decrease in smoking rates and decrease in lung cancer occurrence, strengthen the association between smoking and lung cancer as causal. For the case of use of talcum powder products and ovarian cancer risk, the prevalence of other risk and protective factors (e.g., use of oral contraceptives, hysterectomy, and tubal ligation as protective factors, obesity as risk factor) changed over time in the general population. Therefore, it would be difficult to determine if ovarian

cancer incidence time trends vary by changes in use of talcum powder products. The biology involves, as described below, the migration of talc to the ovaries, the inflammatory process which talc elicits, and the carcinogenetic effects of inflammation.

Experiment: The evidence from randomized controlled trials can provide strong support to observational evidence. However, in many situations, randomized controlled trials are not feasible. In the case of talcum powder products and ovarian cancer risk, a trial would have to be very large, involving 50,000 women or more, followed for decades, to determine effects of use of talcum powder products on risk for ovarian cancer. This is because ovarian cancer is a rare disease and typically takes many years to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type.

Analogy: Bradford Hill states that in some circumstances it would be fair to judge by analogy. Therefore, since some toxic agents such as thalidomide or rubella have been shown to cause birth defects, other drugs or viral exposures may be recognizable as possibly leading to harmful effects to a fetus. Regarding talcum powder products use and ovarian cancer use: since increased inflammation has been associated with increased ovarian cancer risk, and since talc causes an inflammatory response in tissues, this strengthens the link between talcum powder products use and ovarian cancer risk.

Methods Used for this Review

In performing this evidence review and for purposes of my opinions, I first conducted a review of the relevant literature on the epidemiology of ovarian cancer risk in relation to use of talcum powder products, using the same process I use for systematic review articles I write for my academic work. (Chan, Vieira et al. 2014, 2018) I triaged articles by title, then by abstract, and finally by complete paper. As I read the epidemiologic literature, I considered the “Bradford Hill” aspects of causal inference (Hill 1965), as well as causal inference as defined by Rothman (Rothman and Greenland 2005), and weighed the evidence. My search identified studies that both support and do not support my eventual opinion on whether use of talcum powder products can cause ovarian cancer.

I also searched for systematic reviews on the issue of talcum powder product use and risk of ovarian cancer.

I searched in the PubMed database for research studies published in peer-reviewed, PubMed indexed journals, using the following search terms: ("talc" OR "talcum powder") AND ("ovarian cancer" OR "ovarian carcinoma").

The initial search produced 110 references, of which 7 included meta-analyses (Harlow, Cramer et al. 1992, Gross and Berg 1995, Cramer, Liberman et al. 1999, Huncharek, Geschwind et al. 2003, Langseth, Hankinson et al. 2008, Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018), one was a pooled analysis (Terry, Karageorgi et al. 2013), and 33 were reports of original epidemiologic studies that tested the association between talcum powder products and risk of ovarian cancer. In addition, a pooled analysis of four cohort studies was published in 2020 (O'Brien, Tworoger et al. 2020), after the original version of this expert report was prepared, and is now summarized in this version. More recently, two additional meta-analyses were published (Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020, Woolen, Lazar et al. 2022) as well as two additional pooled analyses (Davis, Bandera et al. 2021, Phung, Muthukumar et al. 2022). For this amended report, I repeated the above search to November 2023.

I did not perform a meta-analysis, because excellent meta-analyses of all available studies have been recently published, (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020) and all of the published meta-analyses showed similar relative risk estimates for use of talcum powder products and risk of ovarian cancer. For all of the reviewed studies, I performed data extraction using a standardized data extraction table (see Tables 1-4). I recorded information on the publication year, study design, number of cases, number of controls (for case-control studies), total sample size (for cohort studies), population type, country, risk estimates, confidence intervals, and the type of ovarian cancer. I also indicated whether dose-response relationships were assessed, method used, and results.

In this report, I provide descriptions of the study methods and main study results including risk estimates (odds ratio, relative risk, or hazard ratio). All studies included control for some confounders and presented the risk estimates with adjustment for the confounders. I present below the results from adjustment with the greatest number of variables.

Epidemiologic Evidence on the Association between Talcum Powder Products Use and Ovarian Cancer Risk

Case-control Studies

Schildkraut *et al*. (Schildkraut, Abbott et al. 2016) investigated the association between body powder use and ovarian cancer in African American women in 11 geographic areas of the U.S. Included were 584 cases and 745 controls, in a population-based study. Cases were identified through state or SEER cancer registries, or through hospital gynecologic oncology departments. Controls were randomly selected from the same populations as the cases. Participants were asked in a phone interview whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Women were classified as "regular users" if they reported using any of these powders at least monthly for at least 6 months, and "never users" otherwise. Regular users were asked about frequency and duration of use; use on genital areas, underwear, sanitary napkins, or diaphragms; and use on non-genital areas. Lifetime number of applications was estimated as number of applications per month times number of months used. Occupational exposure (yes/no) was ascertained for a subset of participants. Use of genital powder was associated with a statistically significant 44% increased risk for ovarian cancer (odds ratio 1.44, 95% CI 1.11-1.86).

A dose-response trend was noted: compared with never-users, women who used genital powder less than daily had a 12% increased risk for ovarian cancer, while women who used genital powder daily had a 71% increased risk. The statistical test for trend was significant ($p < 0.01$). Furthermore, a greater number of years used increased risk further: compared with never-users, women who used genital powders for less than 20 years had a 33% increased risk of ovarian cancer, while those who used genital powders for 20 years or more had a 52% increased risk of ovarian cancer. The statistical test for trend was significant ($p = 0.02$). Estimated lifetime number of applications was also related to risk in a dose-dependent manner. Compared with never users, those who used few than 3600 genital powder applications had a 16% increased risk for ovarian cancer, while those who used 3600 or more applications had a 67% increased risk. The statistical test for trend was significant ($p < 0.01$). Risk of both serous and non-serous ovarian cancer increased statistically significantly with any genital powder use by 38% and 63%, respectively (odds ratios, 1.38, 95% CI 1.03-1.85, and 1.63, 95% CI 1.04-2.55, respectively).

Cramer *et al*. (Cramer, Vitonis et al. 2016) reported on association between genital talc use and risk of ovarian cancer in 2,041 cases of ovarian cancer and 2100 controls. Cases were combined from three case-control studies interviewed in 1992-97, 1998-2002, and 2003-2008. Cases were identified from tumor boards and registries in Eastern Massachusetts and Massachusetts. Controls were identified from the same populations as controls. Interviewers asked participants if they "regularly" or "at least monthly" applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or non-genital areas. Type of powder, age begun, years used, and applications per month were ascertained. Lifetime exposure was estimated by multiplying frequency of applications per month by months used, and talc-years were calculated. Participants were then divided into quartiles according to these variables. Participants were also asked if their partners dusted or sprayed powder to their genital or rectal areas. Condom and diaphragm use were ascertained as potential sources of genital talc exposure.

Genital talc use was associated with a statistically significant 33% increased risk of ovarian cancer (odds ratio 1.33, 95%CI 1.16-1.52). Risk decreased with increasing time since last use. There was a clear trend to increasing risk for ovarian cancer with increasing frequency of use: compared with never users, risks for 1-7 days per month, 8-29 days per month, and 30 or more days per month were increased by 17%, 37%, and 46%, respectively, and the trend was statistically significant ($p<0.0001$). Furthermore, as months per year of use increased, risk increased, and the trend was statistically significant ($p=0.006$).

Risk for serous invasive, endometroid invasive, and serous borderline were increased with any genital talc use, by approximately 40%, and all were statistically significant. Risks of serous invasive and endometroid also increased significantly with increased talc-years of use. Risks of serous invasive were increased in both premenopausal and postmenopausal women who used genital products, but the results were only statistically significant in premenopausal women. Premenopausal women and postmenopausal women using hormone therapy had the largest risks associated with talcum powder product use for most types of ovarian cancers.

Wu *et al*. (Wu, Pearce et al. 2015) investigated the associations of risk of ovarian cancer and talcum powder products use and other risk factors. Cases were identified through the SEER population-based University of Southern California cancer registry. A total of 1,701 patients were included; and 2,319 controls were recruited from the cases' neighborhoods using random selection from population lists. In-

person interviews were conducted. To determine use of talcum powder products, women were asked if they ever used talc at least once per month for 6 months or more. (Wu, Pearce et al. 2009) If the response was positive, they were asked whether they had ever used talc in non-perineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use. Use of genital talc for one year or more was associated with a statistically significant 46% increased risk for ovarian cancer (odds ratio 1.46, 95% CI 1.27-1.69). Similar relative risks were seen in non-Hispanic white, Hispanic, and African-American women. A dose-response analysis found that for each 5-year use of genital talc products, risk for ovarian cancer increased by a statistically significant 14% (95% CI 1.09-1.20).

Kurta *et al*. (Kurta, Moysich et al. 2012) published results of a population-based case-control study based in Western Pennsylvania, Eastern Ohio, and Western New York State. A total of 902 cases were enrolled, and 1,802 controls were randomly selected from the general population of those areas. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps. Use of perineal talc increased risk for ovarian cancer by a statistically significant 40% (odds ratio 1.40, 95% CI 1.16–1.69).

Rosenblatt *et al*. (Rosenblatt, Weiss et al. 2011) published results of a population case-control study set in western Washington that investigated the association between genital powder exposure and risk of ovarian cancer. A total of 812 women with ovarian cancer were identified through a population-based cancer registry and interviewed. A total of 1,313 controls were selected at random from the western Washington population. Sources of genital powder were ascertained, including direct perineal application, use on sanitary napkins and diaphragms, and use of deodorant vaginal spray. For powder use on sanitary napkins and use of vaginal deodorant sprays, the authors recorded the total number of months or years in which these products were used. For use of perineal powder, the investigators recorded the age began and ended, number of weeks or months of use per year, and average days per week used. Study participants were also asked about the types of powder used, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The authors then calculated the lifetime duration of use, and estimated lifetime number of applications. Perineal use of powder was associated with a non-statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 0.97-1.66). The risk for borderline ovarian tumors was statistically significantly raised by 55% (odds ratio, 1.55, 95% CI 1.02-2.37), whereas risk for invasive ovarian cancers was increased by a non-statistically

significant 27% (odds ratio 1.27, 95% CI 0.87-1.58). Use of powder on either sanitary napkins or diaphragms did not increase risk. Use of vaginal deodorant spray increased risk by a non-statistically significant 15% (odds ratio 1.15, 95% CI 0.85-1.56). None of the dose-response or time variables (years of use, lifetime number of applications, age at first use, age at last use, calendar year of first use, time since first and last uses) showed evidence of increasing relative risk of ovarian cancer with increasing level of exposure to talcum powder products. Similarly, there was no evidence of increased risk for ovarian cancer with increasing dose of powder use on sanitary napkins, or of vaginal deodorant sprays. Use of perineal powder increased risk for mucinous borderline, serous borderline, endometrioid, and other non-mucinous ovarian cancers by 47% to 78%, but none of the odds ratios was statistically significant.

Wu *et al.* (Wu, Pearce et al. 2009) presented results of a case-control study of ovarian cancer with 609 cases and 688 controls. Risk of ovarian cancer among users of talcum powder products in the perineal area was increased by 53% (odds ratio 1.53, 95% CI 1.13-2.09). Risk of serous ovarian cancer was also significantly elevated (odds ratio 1.70, 95% CI 1.27-2.28). A statistically significant trend to increased risk with lifetime numbers of applications was observed. Compared with no use, odds ratios for those with $\leq$ 5200, >5200 - $\leq$15,600, >15,600 - $\leq$52,000, and > 52,000 applications were 1.2, 1.38, 1.34, and 1.99, respectively (p_{trend} = 0.0004).

Moorman *et al*. (Moorman, Palmieri et al. 2009) published data from a population-based case-control study in White and Black women. In total, 1114 cases and 1086 controls were interviewed. They found no association of genital talcum powder product use and risk for ovarian cancer in Whites (odds ratio 1.04, 95% CI 0.82-1.33), and a non-statistically significant increased risk in Blacks (odds ratio 1.19, 95% CI 0.68-2.09). Neither dose-response nor effects by histologic subtype were addressed.

Merritt *et al*. (Merritt, Green et al. 2008) published results from an Australian-wide population-based case-control study on talcum powder products and risk of ovarian cancer. Included were 1,576 women with ovarian cancer and 1,509 population-based controls. Women provided information on self-administered questionnaires. They were asked if they had ever used powder or talc in the genital area, on underwear, or on sanitary pads or diaphragms. They were also asked about age at first use and years of talc use in these areas. Duration of talcum powder use prior to and after surgical sterilization was calculated, and all analyses were limited to the time when the fallopian tubes would have been patent.

Use of talc elsewhere was also collected. Ever use of talc in the perineal region was associated with a statistically significant 17% increased risk for ovarian cancer (odds ratio 1.17, 95% 1.01-1.36). The increase was strongest for serous (odds ratio 1.21, 95% CI 1.03-1.44), but was also seen for endometrioid (odds ratio 1.18, 95% CI 0.81-1.70). A statistically significant dose-response trend for years of perineal talcum powder use prior to surgical sterilization was seen for all cases combined (p=0.021) and for serous ovarian cancer (p=0.022). While not statistically significant, increasing years of use was associated with increased risk of mucinous and endometrioid ovarian cancers.

Mills *et al*. (Mills, Riordan et al. 2004) reported on a population-based case-control study in 22 counties of Central California. A total of 256 cases were recruited from cancer registries and interviewed, and 1,122 population-based controls were randomly selected and interviewed. Women were asked the following about use of talcum powder: use in the genital area, years of use, frequency of use, and total duration of use. Ever use of perineal talc statistically significantly increased risk for ovarian cancer by 37% (odds ratio 1.37, 95% CI 1.02-1.85). There was a statistically significant trend found in the dose-response analysis of frequency of use; women using talc 4-7 times per week had a 74% increased risk for ovarian cancer (p=0.015). There was an indication of trend with duration of use up to 4-12 years, although number of years beyond that did not increase risk further. A similar relationship was found for cumulative dose (frequency times duration). Risk of serous ovarian cancer was also statistically significantly elevated (odds ratio 1.77, 95% CI 1.12-2.81).

Ness *et al*. (Ness, Grisso et al. 2000) recruited women with ovarian cancer ascertained from 39 hospitals in Eastern Pennsylvania, Southern New Jersey, and Delaware. A total of 767 cases of ovarian cancer were interviewed, along with 1,367 population-based controls. Women were asked if they ever used talc, baby, or deodorizing powder at least once per month for 6 or more months in their genital or rectal area, on sanitary napkins, on underwear, on a diaphragm or cervical cap, or on non-genital areas. They also were asked about male partner use of talc to the genital area or underwear. Compared with never-users, women who used talc in genital/rectal areas had a statistically significant 50% increased risk for ovarian cancer (odds ratio 1.5, 95% CI 1.1-2.0). Those who used it on sanitary napkins had a statistically significant 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.1-2.3). Use on underwear increased risk by a statistically significant 70% (odds ratio 1.7, 95% CI 1.2-2.4). Use on a diaphragm/cervical cap or by a male partner did not increase risk. Among those who used in the

genital/rectal or other body areas, there was no evidence of increasing risk with increasing numbers of years of use.

Cramer *et al.* (Cramer, Liberman et al. 1999) published results of a population-based case-control study with 563 cases of ovarian cancer and 523 controls. Risk of ovarian cancer among women with perineal talcum powder product exposure was increased 60% compared with non-exposed (odds ratio 1.6, 95% CI 1.18-2.15). Risk of invasive serous ovarian cancer was significantly increased (odds ratio 1.7, 95% CI 1.22-2.39). No dose-response effect, as defined by duration, was seen.

Wong *et al*. (Wong, Hempling et al. 1999) conducted a hospital-based case-control study in Buffalo, NY, comparing 499 patients with ovarian cancer and 755 patients with non-gynecological malignancies. No details were given on how talcum powder product use was ascertained, but women were queried on site of talc use (sanitary napkin vs. genital/thigh area) and duration of use. Compared with non-users, those who used on sanitary napkins or genital/thigh areas had no increase in risk for ovarian cancer. Furthermore, there was no apparent trend toward greater risk with longer duration of use. Finally, there was a non-statistically significant 20% increased risk of serous ovarian cancer with talcum powder product use (odds ratio 1.2, 95% CI 0.7-2.1).

Godard *et al*. (Godard, Foulkes et al. 1998) studied risk of sporadic (101 cases) or familial (51 cases) ovarian cancer according to perineal talc use compared with 152 control in Montreal, Canada. Cases were diagnosed at one of two teaching hospitals; controls were randomly selected from the population. Talc use questions were not detailed in the paper, but the variable of “ever” versus “never” perineal use of talc was reported. Women who had ever used perineal talc had a 2.49 times greater risk of developing any ovarian cancer (relative risk 2.49, 95% CI 0.94-6.58, p=.066), which was marginally statistically significant. The relative risk for sporadic ovarian cancer was 2.45 (95% CI 0.85-7.07, p=0.098), and for familial ovarian cancer it was 3.25 (95% CI 0.85-12.4, p=.084).

Green *et al*. (Green, Purdie et al. 1997) included 824 Australian women with ovarian cancer who were identified through cancer registries, as well as 855 population-based controls. No details were provided on the specific questions posed regarding talc use, but perineal use was ascertained, as well as duration and ages/years used. Women who had ever used talc in the perineal region had a statistically significant 30% increased risk for ovarian cancer (relative risk 1.3, 95% CI 1.1-1.6). The authors investigated

whether a history of surgical sterilization affected this relative risk (the rationale being that women who are surgically sterilized would have lower chance of talc migrating up to the ovaries). They found that compared with women who had neither used talc nor had surgical sterilization, risk was highest among talc users without surgery (relative risk 1.3, 95% CI 1.0-1.7) and lowest among women with a history or tubal sterilization or hysterectomy who had not applied talc to the perineum (relative risk 0.6, 95% CI 0.5-0.84). No dose-response relationship by duration of use was found.

Cook *et al*. (Cook, Kamb et al. 1997) reported on a population-based case-control study including 313 cases of ovarian cancer identified through a cancer registry and 422 population-based controls in Western Washington. Women were queried about storing diaphragms in powder, dusting perineal areas with powder after bathing, powdering sanitary napkins, and using genital deodorant sprays (which may contain aerosolized powder). Women were further asked about duration and frequency of powder application and about types of powder applied. There was a statistically significant 50% increase in risk of ovarian cancer associated with use of any of the genital powder applications (perineal application, sanitary napkins, genital deodorant sprays, diaphragms) (relative risk 1.5, 95% CI 1.1-2.0). The risk was highest, and statistically significant, in those women who dusted perineal areas with powder (relative risk 1.8, 95% CI 1.2-2.9). Compared with never users of genital deodorant sprays, women who used these products for 12 months or less had a relative risk for ovarian cancer of 1.5, while those who used them for more than 12 months had a relative risk of 2.7. Compared with never users of genital deodorant sprays, women who used 500 lifetime applications or less of genital deodorant sprays had a relative risk for ovarian cancer of 1.7, while those who used more than 500 applications had a relative risk of 2.6. Both of these dose-response trends were statistically significant ($p < 0.05$). None of the other types of perineal talcum powder product use showed trends to greater risk with greater estimated duration used or applications. The authors then categorized powders into specific types: cornstarch, talcum powder, baby powder, deodorant powder, and scented body/bath powder (assuming talcum powder was likely a constituent of the latter three as well). Exclusive use of cornstarch, or of deodorizing powder, was not associated with increased risk for ovarian cancer, but the numbers of cases were very small (5 and 9, respectively). Exclusive use of other types of powder increased risk between 20 and 60 percent, but the results were not statistically significant. Risk for serous ovarian cancers was statistically significantly increased by 70% in women who ever used any genital powder (relative risk 1.7, 95% CI 1.1-2.5). The relative risk for “other tumors” among ever users was 1.8 (95% CI 1.1-2.8), while risks for mucinous or endometrioid tumors were not increased in genital powder users.

Chang *et al*. (Chang and Risch 1997) reported on the association between talcum powder product use and risk of ovarian cancer in a population-based case-control study in Ontario, Canada. A total of 450 patients with borderline or invasive ovarian cancer and 564 population controls were interviewed. Women were asked about regular talc use and type of talc used, as well about duration and frequency of use. Women were queried about regular application of talc to the perineum and about use of talc on sanitary napkins. Use of cornstarch on the perineum and sanitary napkins was also ascertained. Women with any regular talc exposure had a statistically significant 42% increased risk of developing ovarian cancer (odds ratio 1.42, 95% CI 1.08-1.86). Use of cornstarch was not associated with increased risk, although this was a very uncommon exposure in this study. Use of talc on sanitary napkins increased risk to a lesser degree (odds ratio 1.26, 95% CI 0.81-1.96), as did use of talc only in the perineal area (odds ratio 1.31, 95% CI 1.00-1.73). A dose-response trend was seen: per 10 years of use of talc to the perineal area, risk of ovarian cancer increased by 6% (odds ratio 1.06, 95% CI 0.99-1.14). Frequency of use per month, however, did not show a dose-response trend. Use before and after 1970 showed almost identical odds ratios. Risk was higher prior to tubal ligation/hysterectomy than after either procedure. Risk was increased for all types of ovarian cancer included (invasive, borderline, serous, mucinous, and endometrioid). Only for invasive cancer was the odds ratio statistically significant, likely due to the larger numbers of cases in that category.

Shushan *et al*. (Shushan, Paltiel et al. 1996) published results of a population-based case-control study in Israel, looking at the association between talcum powder product use and risk of invasive or borderline ovarian cancer. A total of 200 cases, identified through a cancer registry, were interviewed, as were 408 controls selected randomly from the same population. Details of the talcum powder product use on the standardized questionnaire were not provided. Women who reported using talc “moderate to a lot” versus “never or seldom” had twice the risk of developing ovarian cancer, and the result was statistically significant (odds ratio 2.0, p=0.04).

Purdie *et al*. (Purdie, Green et al. 1995) studied the association between talcum powder product use and ovarian cancer risk in 3 Australian states. Cases were recruited from registries at three oncology treatment centers, and controls were chosen randomly from the general population. The details of the interview items on talc were not provided. Women who used talc around the perineum or abdomen had a statistically significant 27% increased risk for ovarian cancer (odds ratio 1.27, 95% CI 1.04-1.54).

Cramer *et al.* (Cramer and Xu 1995) published results of two case-control studies, in which a total of 450 women diagnosed with ovarian cancer in Boston, MA area hospitals, and 454 controls selected from the general population, were interviewed. Use of talc "in genital hygiene" was associated with a 60% increased risk for ovarian cancer (odds ratio 1.6, 95% CI 1.2-2.1).

Tzonou *et al*. (Tzonou, Polychronopoulou et al. 1993) conducted a hospital-based case-control study in Athens, which included 189 women with ovarian cancer and 200 hospital visitor controls. No information was provided on how talcum powder product use was ascertained, other than that women were interviewed about whether or not they used of talc in the perineal area. There was little evidence of an association: the relative risk for ovarian cancer in those who said "yes" versus "no" to perineal talc use was 1.05 (95% CI 0.28-3.98). However, only 6 cases and 7 controls reported using talc in the perineal area.

Rosenblatt *et al*. (Rosenblatt, Szklo et al. 1992) published results of a hospital-based case-control from the Baltimore, MD area. A total of 77 cases of ovarian cancer and 46 controls, who were treated for non-gynecologic/non-malignant diseases, were included. Participants were interviewed about presence and length of genital fiber and respiratory fiber exposure. Fiber exposure was defined as exposure to asbestos, talc, and fiberglass. Dose of exposure was calculated as number of years of each type of genital or respiratory exposures from all sources, and only exposure prior to tubal ligation (for women who had that procedure) was counted. Use of genital talc was associated with a 70% increased risk (odds ratio 1.7, 95% CI 0.7-3.9). Use of talc on sanitary napkins resulted in almost a 5-fold statistically significant increase in risk of ovarian cancer (odds ratio 4.8, 95% CI 1.3-17.8). Talc use on diaphragms tripled risk for ovarian cancer (odds ratio 3.0, 95% CI 0.8-10.8). The odds ratios for these latter two exposures were not statistically significant. Women who had exposure years above the median had more than double the risk of ovarian cancer compared with women with lower exposure years (odds ratio 2.4, 95% CI 1.0-5.8).

Chen *et al.* (Chen, Wu et al. 1992) interviewed 112 women with ovarian cancer and 224 community controls in China. No information was provided about how women were asked about talcum powder product use prior to 3 years before diagnosis (for cases) and a comparable date in controls. Seven cases

and 5 controls reported using "dusting powder" to the lower abdomen and perineum for 3 or more months, giving a relative risk of 3.9 (95% CI 0.9-10.6).

Harlow *et al.* (Harlow, Cramer et al. 1992)published a case-control study with 235 cases of ovarian cancer and 239 controls. The authors found a 50% increased risk of ovarian cancer in women who had ever versus never used talcum powder products in the perineal area with marginal statistical significance (odds ratio 1.5, 95% CI 1.00-2.1). Risk of serous cancer was similarly increased (odds ratio 1.4, 95% CI 0.9-2.2). Risk by number of lifetime applications indicated a dose response effect. Compared with no use, odds ratios for those with < 1000, 1000 – 10,000, and > 10,000 were 1.3, 1.5, and 1.8, respectively (p_{trend} = 0.09).

Booth *et al*. (Booth, Beral et al. 1989) reported on a hospital-based case-control study conducted in 15 hospitals in the UK. A total of 235 cases with ovarian cancer and 451 controls were interviewed and asked about monthly experiences from age 16 to 45 years. Frequency of exposure to perineal talc was ascertained. Compared with never-users, women who used genital talc rarely, monthly, weekly, and daily, respectively, had relative risks for ovarian cancer of 0.9, 0.7, 2.0, and 1.3, respectively, and the trend was statistically significant (p=0.05). Cases and controls did not differ by percentage who stored diaphragms in talc.

Harlow *et al*. (Harlow and Weiss 1989) interviewed 116 women with serous or mucinous borderline ovarian cancer identified through a Western Washington population-based cancer registry, as well a population-based sample of 158 control women. The authors used an open-ended question asking women to specify the types of powder they used for perineal application after bathing, on sanitary napkins, and on diaphragms. Powder was categorized as baby, deodorizing, other/unspecified talcum, or cornstarch. There was no association between perineal use in general and risk for borderline ovarian cancer, but women who reported using powder on sanitary napkins had a relative risk of 2.2 (95% CI 0.8-19.8) compared with nonusers. Women who used deodorizing powders had a statistically significant relative risk of 2.8 (95%CI 1.1-11.7). No data were presented on frequency or duration of use.

Whittemore *et al*. (Whittemore, Wu et al. 1988) included 188 ovarian cancer cases (identified through 7 hospitals in the San Francisco, CA area, and 539 controls (of which approximately half were hospital controls and half were population-based controls). Women were asked whether they had ever use

talcum powder on the perineum, on sanitary pads, or on diaphragms, and about frequency and duration of use. Women who reported using talcum powder to the perineum had a non-statistically significant 45% increased risk for ovarian cancer (relative risk 1.45, 95% CI 0.81-2.60). Use on sanitary pads was associated with a non-statistically significant 38% reduced risk, and use on diaphragms was associated with a non-statistically significant 50% increased risk. The relative risk for ovarian cancer increased with increasing applications of talc per month; relative to nonusers, the relative risk for 1-20 times per month was 1.27, and the relative risk for 20 or more times per month was 1.45. None of these values was statistically significant. The increased relative risk was apparent for women who had never had tubal ligation or hysterectomy, but not for women who had had one of these procedures. Compared with non-users, women with 1-9 years of use had a relative risk of 1.6 (95% CI 1.00-2.57), but women with greater years of use had only a relative risk of 1.11 (95% CI 0.74-1.65).

Hartge *et al*. (Hartge, Hoover et al. 1983) provided a brief report on a small hospital based case-control study of ovarian cancer, which included 135 cases and 171 controls from the Washington, DC area. No information was provided on how the talc exposure was ascertained. The authors found that women who reported genital talc use had a relative risk of 2.5 compared with never users (95% CI 0.70-10.0), but this analysis was based on only 7 cases and 3 controls.

Cramer *et al.* (Cramer, Welch et al. 1982) published the first study to look at the association between talcum powder product use and risk of ovarian cancer. This population-based study found an odds ratio of 1.92 (95% CI 1.27-2.89) for ever use of perineal talcum powder products in the perineal area. Dose-response was not addressed.

Summary of Case-control Studies

These 28 case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Sample sizes ranged from 77 to 2041 cases, with comparable numbers of controls. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users (Cramer, Welch et al. 1982, Hartge, Hoover et al. 1983, Whittemore, Wu et al. 1988, Booth, Beral et al. 1989, Chen, Wu et al. 1992, Harlow, Cramer et al. 1992, Rosenblatt, Szklo et al. 1992, Cramer and Xu 1995, Purdie, Green et al. 1995, Shushan, Paltiel et al. 1996,

Chang and Risch 1997, Cook, Kamb et al. 1997, Green, Purdie et al. 1997, Godard, Foulkes et al. 1998, Cramer, Liberman et al. 1999, Ness, Grisso et al. 2000, Mills, Riordan et al. 2004, Merritt, Green et al. 2008, Wu, Pearce et al. 2009, Rosenblatt, Weiss et al. 2011, Kurta, Moysich et al. 2012, Wu, Pearce et al. 2015, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value $\leq$ 0.05) (Cramer, Welch et al. 1982, Cramer and Xu 1995, Purdie, Green et al. 1995, Shushan, Paltiel et al. 1996, Chang and Risch 1997, Cook, Kamb et al. 1997, Green, Purdie et al. 1997, Cramer, Liberman et al. 1999, Ness, Grisso et al. 2000, Mills, Riordan et al. 2004, Merritt, Green et al. 2008, Wu, Pearce et al. 2009, Kurta, Moysich et al. 2012, Wu, Pearce et al. 2015, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be needed to have power to detect a statistically significant result (Hartge, Hoover et al. 1983, Whittemore, Wu et al. 1988, Booth, Beral et al. 1989, Chen, Wu et al. 1992, Harlow, Cramer et al. 1992, Rosenblatt, Szklo et al. 1992, Godard, Foulkes et al. 1998). It is important to note that while the 8 studies did not have statistically significant results, they provide relevant data because their relative risk estimates were consistent with the 16 studies that showed statistically significant results. (Rothman and Greenland 2005)

Both population-based and hospital-based studies were represented in the literature on use of talcum powder products and risk of ovarian cancer, and odds ratios/relative risks were similar across the two classes of studies. Earlier studies were less likely to address dose-response relationships, or to investigate effects of talcum powder product use on specific histologic subtypes of ovarian cancer. Most studies were limited to white women; later studies included larger numbers of Black women as well as Asian and Latina women.

The larger, and more recent studies, however, added important information on dose-response relationships and on risk of particular histologic subtypes of ovarian cancer. Many of the 28 studies found evidence of a dose-response effect (Whittemore, Wu et al. 1988, Booth, Beral et al. 1989, Harlow, Cramer et al. 1992, Rosenblatt, Szklo et al. 1992, Cramer, Liberman et al. 1999, Merritt, Green et al. 2008, Wu, Pearce et al. 2009, Wu, Pearce et al. 2015, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016). Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. The later studies determined that some risk of some subtypes, particularly serous ovarian cancer, were more highly related to use of talcum powder products.

Taken together, the case-control studies, conducted over 40 years, provide consistent and replicated evidence of increased risk of ovarian cancer with perineal exposure to talcum powder products, with evidence of a dose-response. They support the conclusion that talcum powder products can cause ovarian cancer.

Prospective Cohort Studies

The Sister Study

The first Sister Study cohort analysis included 135 cases of women with ovarian cancer, 7 cases of fallopian tube cancer, 4 cases of peritoneal cancer, and 8 cases with unknown primary site. (Gonzalez, O'Brien et al. 2016) Of the total 154 cases, only 96 were confirmed by medical records or death certificate. Women were recruited to the cohort from across the United States from 2003-2009. An analysis of talcum powder products use and ovarian cancer risk, published in 2016, included 41,654 women who reported having at least one ovary and no history of ovarian cancer at study entry, from among 50,884 women aged 35-74 years at study enrollment with at least one sister who had been diagnosed with breast cancer.

Talcum powder products use for the 12 months prior to study entry was ascertained by self-administered questionnaires. Questions included frequency of genital talcum powder products use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1-3 times/month, used 1-5 times/week, or used more than 5 times/week. Only a dichotomous variable—use/nonuse—was used in the analysis. Ovarian cancer cases were identified by yearly follow-up questionnaires; no updates on talc use were included. The median follow-up of study participants was only 6.6 years.

Contrary to all of the other epidemiologic studies, perineal talc use was associated with a non-statistically significant 27% decreased risk of developing ovarian cancer (hazard ratio 0.73, 95% CI 0.44 - 1.2). Of note, the 95% CI's included 1.2, so the true relative risk in this cohort could have been in the range of the other studies. Use of talcum powder products during ages 10-13 years showed a non-

statistically significant 10% increase in risk (hazard ratio 1.1, 95% CI 0.74, 1.7). No data on risk by ovarian cancer subtype were presented.

As noted above, the misclassification of exposure in the Sister Study (because adult talcum powder product use was ascertained only for the year prior to study entry resulted in significant under-estimation of exposure) likely caused significant bias in the estimated hazard ratio of ovarian cancer associated with genital exposure to talcum powder products.

Updated Sister Study Analyses

On May 15, 2024, the Journal of Clinical Oncology (the official journal of the American Society of Clinical Oncology) published a new investigation from the NIH Sister Study cohort of genital exposure and ovarian cancer risk (O'Brien, Wentzensen et al. 2024) as well as an accompanying editorial. (Harris, Davis et al. 2024)

O'Brien and colleagues at the NIH National Institute for Environmental Health Sciences stated that the objective of their study was to "re-evaluate the associations between intimate care product use and incidence of hormone-related cancers, expanding on previous analyses, by incorporating newly diagnosed ovarian and uterine cancers, adding breast cancer as an outcome, and integrating new data on lifetime use of douche and genital talc." They go on to state, "Because the newly acquired exposure data were susceptible to differential missingness by cancer status, we used quantitative bias analysis to estimate effects under several missingness assumptions. When examining the association between genital talc use and ovarian cancer, we additionally evaluated the potential impact of recall bias."

The authors laid out the premises that led to this objective: 1) Intimate care products may contain endocrine-disrupting chemicals, other known or suspected carcinogens such as volatile organic compounds, and asbestos; 2) Genital powder is of concern because of "the natural co-occurrence of talc and asbestos," "..recent surveillance identified asbestos particles in certain talc products," and "Use of powder in the genital area could plausibly promote carcinogenesis through mechanisms other than direct contact with asbestos, including exposure to other chemicals or irritation and inflammation of the reproductive tract;" and 3) "…prospective studies tend to have small case numbers and simplified

exposure assessments, resulting in low statistical precision and increased likelihood of nondifferential exposure misclassification."

As described in my original report, the Sister Study includes 50,884 women without breast cancer, enrolled at age 35-74 years between 2003-9, who had a sister previously diagnosed with breast cancer. Women were excluded from the new analyses if there were missing data for key covariates. Also excluded from the new analyses were women who had suspected ovarian cancer before enrollment or had a history of removal of both ovaries (who would then have little risk for ovarian cancer).

The first questionnaire completed by participants when they enrolled in the Sister Study collected data on exposure to genital talc focused on the 12 months before enrollment and on use during ages 10-13 years. Women were asked how frequently they applied talcum powder to a sanitary napkin, underwear, diaphragm, cervical cap, or directly to the vaginal areas. During follow-up, between 2017-2019, women completed another set of questionnaire items related to talc exposure. They were asked if they ever used talc, and if yes, their age at first and most recent use, and their frequency of use during each decade. Therefore, this second round of questioning collected lifetime exposure to genital talc, which is the first time that a cohort study has collected this information. (In contrast, many of the case-control studies did collect lifetime exposure, for example: Chang and Risch 1997, Cook, Kamb et al. 1997, Mills, Riordan et al. 2004, Wu, Pearce et al. 2009, Rosenblatt, Weiss et al. 2011, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016.

The investigators calculated relative risks (hazard ratios) for use of genital talc in several ways. First they looked at risk with ever use versus never use. Then they considered effects of frequent use, long-term use, and use in particular life periods (teens, 20s, 30s, and in the 12 months prior to enrollment).

Women were followed through September 2021 for incidence of ovarian cancer (uterine and breast cancers were additional outcomes in this paper). A total of 35% of women reported ever using genital talc during their lifetime. (This compares with the 14% of the cohort reporting ever use in the first Sister Study publication which relied on only data for the year before enrollment to classify women as users or nonusers.) During this period a total of 292 cases of ovarian cancer occurred. Of these 292, 30 occurred after they completed the follow-up questionnaire, and therefore provided prospective information for both pre-enrollment and follow-up questions on genital talcum powder exposure.

The investigators corrected for missing data with a technique called “multiple imputation,” which is a standard statistical technique to correct for missing data. (Li, Stuart et al. 2015) O’Brien used a standard statistical program for multiple imputation and provides the exact program used (SAS PROC MI). This is the same program that was used to account for missing data in several of my studies. (Mason, Xiao et al. 2013) (Imayama, Ulrich et al. 2012) As described in a JAMA Guide to Statistics and Methods article, “it is important to not exclude cases with missing information.” (Li, Stuart et al. 2015) Furthermore, the guide states that multiple imputation corrects for problems introduced when investigators analyze only participants without missing values. For example, excluding cases with missing information makes the assumption that those missing were completely at random. As these JAMA statistical authors state, multiple imputation is not “making up data” but rather “Multiple imputation fills in missing values by generating plausible numbers derived from distributions of and relationships among observed variables in the data set.” Furthermore, they point out that through multiple imputation, the problems of reduced sample size from missing data can be overcome, which increases study power to detect statistically significant associations. Regarding their analyses using multiple imputation to estimate genital talc exposure, O’Brien et al. authors state, “…we consider it our best estimate of the true association in the absence of recall or other unknown biases.” (O'Brien, Wentzensen et al. 2024)

Out of the 49,806 women in the analytic cohort, 292 developed ovarian cancer during follow-up [note this is larger than previous publications - 154 in 2016 (Gonzalez, O'Brien et al. 2016) and 220 in the 2020 pooled analysis (O'Brien, Tworoger et al. 2020), which gives this study greater power to detect statistically significant associations. With all lifetime genital talc exposure data included from both questionnaires, and multiple imputation to correct for missing data, ever use of genital powder was positively associated with ovarian cancer (hazard ratio = 1.82, 95% CI 1.36-2.43). This indicates almost a doubling of risk of ovarian cancer with exposure to genital talc, a finding that was statistically significant. Risk for neither breast nor uterine cancer was increased with genital talc powder exposure. The authors presented other scenarios: 1) no correction for missing data, hazard ratio 1.07 (95% CI 0.84-1.35); 2) assume unexposed if reported no use at enrollment and missing in follow-up, hazard ratio 1.17 (95% CI 0.92-1.49); and 3) assume exposed if unexposed at enrollment and missing data from follow-up (hazard ratio 3.34, 95% CI 2.51-4.44).

With the additional data collection, the authors were able to assess dose-response relationships between genital talc exposure and ovarian cancer risk. For dose-response, they looked at frequency of use, duration of use, and use during specific life periods (teens, 20s, 30s, and the 12 months before enrollment into the Sister Study). They also looked at associations of ever use of genital talc with risk of specific ovarian cancer subtypes.

Data on dose-response were presented with: 1) multiple imputation to correct for missing data plus no recall bias correction; and 2) multiple imputation with recall bias correction. Risk of ovarian cancer increased regardless of type of analyses. With multiple imputation correction, compared with never use, those with “sometimes use” and “frequent use” had hazard ratios of 1.56 and 1.99, respectively. Confidence intervals did not include 1.0, and therefore were deemed statistically significant. This means that frequent use of genital talcum powder products doubled risk of ovarian cancer. The p test for trend (a statistical test for dose-response) was highly significant at $p<0.001$. Similarly, dose-response analyses with multiple imputation with recall bias correction yielded hazard ratios of 1.18 and 1.81 for “sometimes use” and “frequent use” respectively, with a p test for trend of 0.001. Therefore, with recall bias corrected the elevated risk for ovarian cancer is almost as high as for the recall bias uncorrected analyses.

The authors looked at short-term use (1 decade only) and long-term use (2 or more decades of use). Data on duration were presented with: 1) multiple imputation to correct for missing data plus no recall bias correction; and 2) multiple imputation with recall bias correction. Risk of ovarian cancer increased regardless of type of analyses. With multiple imputation correction, compared with never use, those with “short-term use” and “long-term use” had hazard ratios of 1.48 and 2.20, respectively. Confidence intervals did not include 1.0, and therefore were deemed statistically significant. This means that long-term use of genital talcum powder products more than doubled risk of ovarian cancer. The p test for trend (a statistical test for dose-response) was highly significant at $p<0.001$. Similarly, duration of use analyses with multiple imputation with recall bias correction yielded hazard ratios of 1.17 and 2.01 for “short-term use” and “long-term use” respectively, with a p test for trend of 0.001. Therefore, with recall bias corrected the elevated risk for ovarian cancer is almost as high as for the recall bias uncorrected analyses.

The investigators looked at risk of ovarian cancer with genital talc exposure by histologic type. They looked separately at serous versus nonserous tumors. Similar to results in other studies, risk of serous tumors was increased to a higher degree with genital talc than were nonserous tumors (although both were increased. Correcting for recall bias, the risk for serous cancer was 62% increased in women who ever used genital talc (hazard ratio 1.62, 95% CI 1.06-2.48), and the risk for nonserous tumors was increased by 29% (hazard ratio 1.29, 95% CI 0.79-2.09).

The investigators also compared results of ovarian cancer risk for the cancers overall and for those that were medically confirmed. The risk for medically confirmed ovarian cancer was even higher than for the ovarian cancers overall. Specifically, the risk for medically confirmed cancers (226 women) was increased 46% in those who had used genital talc (hazard ratio 1.46, 95% CI 1.06-2.02); the risk for all ovarian cancers combined (292 women) was increased 40% in genital talc users (hazard ratio 1.40, 95% CI 1.04-1.89).

Patency of the reproductive tract has been assessed as a factor that can modify the association between genital talcum powder exposure and ovarian cancer. Talc applied to the genital area can move through the vagina, cervix, uterus, and fallopian tubes to reach the ovaries and fallopian tubes (ovarian cancers can begin in either structure). Procedures and conditions that close off one or more parts of this route would reduce the chance of talc being moved upward, including surgical removal of the fallopian tubes, tubal ligation for contraception, and hysterectomy. The investigators looked at ever versus never use of genital talc while the reproductive tract was patent and found a hazard ratio (relative risk) of 1.55 (95% CI 1.14-2.09). The investigators looked at ever versus never use of genital talc after hysterectomy or tubal ligation and found a hazard ratio (relative risk) of 1.38 (95% CI 0.69-2.75). Therefore, risk was elevated for both situations, but was higher with patent reproductive tracts.

The investigators also adjusted analyses of genital talc exposure for douche exposure, and found no change in hazard ratio (relative risk) compared with non-adjusted analyses, although the confidence intervals moved from non-significant 38% increased risk with genital talc use but no douche use (hazard ratio 1.38 (95% CI 0.90 -2.13) to significant with douche adjustment (hazard ratio 1.4 (95% CI 1.04-1.90). The difference in statistical significance was likely due to numbers of cases included in the analyses (20 versus 54), with larger number of cases driving the confidence intervals to not include 1.0. Of note, the Sister Study investigators have opined that douching may propel talc products up through the

reproductive tract for those women who use both products: “We speculate that the process of douching may help the ascension of talc particles further up into the reproductive tract...” (Ogunsina, Sandler et al. 2023)

In contrast to the hazard ratios (relative risks) observed for ever use during lifetime, or for specific periods of use by decade (e.g. 20s, 30s), use in the year before enrollment was not associated with increased ovarian cancer risk (hazard ratios with and without recall bias correction were 0.83 and 0.91, respectively). These results highlight the critical importance of ascertaining use over a woman’s lifetime in order to determine risk of ovarian cancer with genital exposure to talcum powder products.

These new data and analyses from the Sister Study cohort do several things:

1) These analyses are an update of the Sister Study cohort, with more cases accrued over a longer period of follow-up than its previous publications. This results in a more stable estimate of hazard ratios (relative risks), with more power to detect statistically significant associations. The relative risk now shows an 82% statistically significant increased risk of ovarian cancer with genital talc exposure in this cohort, i.e., almost a doubling of risk;
2) The analyses assessed ovarian cancer risk from lifetime exposure to genital talc, whereas previously the data referred only to the one year before study entry when women were 35-74 years of age, and/or that at age 10-13 years;
3) These analyses proved that recall bias does not explain the relative risks seen for ovarian cancer with genital talc exposure over decades of research around the world;
4) The resulting hazard ratio (relative risk) for ever vs never use during lifetime (1.82, 95% confidence interval 1.36 to 2.43, statistically significant) is consistent and even higher than that seen in case-control studies which when combined in pooled studies and meta-analyses show relative risks of 1.24-1.35 (statistically significant). (Terry, Karageorgi et al. 2013, Davis, Bandera et al. 2021)(Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019)

The authors state that “Overall, our findings support the hypothesis that there is a positive association between genital talc use and ovarian cancer incidence. If the underlying biological mechanisms and causal agents can be confirmed, interventions and policies designed to limit exposure to the harmful components of intimate care products have the potential to reduce ovarian cancer incidence.”

These new data and analyses from the Sister Study prospective cohort study add strength to aspects of my Bradford-Hill causal analysis, including:

Strength of the association and statistical significance: The analyses for this study correct for potential biases and missing data by using standard statistical techniques. In analyses that corrected for recall bias, the authors found almost a doubling of risk (hazard ratio [relative risk] 1.81, 95% CI 1.29-2.53) in women who frequently used genital talc (p for trend = 0.001). Hazard ratios close to or over 2.0 were observed with use of genital talc for 2 or more decades (hazard ratio 2.01, 95% CI 1.39-2.91), and with use of genital talc in the women's 20s (hazard ratio 1.88, 95% CI 1.37-2.57) and in their 30s (hazard ratio 2.08, 95% CI 1.5-2.89).

Consistency of the association: The results of this cohort study show high consistency with results from case-control, pooled analyses, and meta-analyses, in showing increased risk of ovarian cancer with genital talc exposure. Similar to these other studies that had sufficient power (driven by numbers of cases in the studies), results were statistically significant (i.e., confidence intervals did not include 1.0). Further consistency was seen with the high risks of serous ovarian cancer, although elevated risks were also seen for nonserous cancers.

Specificity of the association: In this study, genital talc exposure was not associated with risks for breast or uterine cancer. If the results were due to recall bias with the follow-up questionnaire, it would be expected that the relative risks for these cancers would also be elevated, but the increased risks were limited to ovarian cancer.

Biologic gradient/ dose-response: Because this study included data on lifetime use of genital talc, including frequency and duration, a more accurate picture of dose-response was possible. With correction for recall bias, the results showed that compared with never use, those with "short-term use" and "long-term use" had hazard ratios of of 1.17 and 2.01, respectively, with a p test for trend of 0.001. This shows clearly that increased exposure to genital talc showed increased risk, which was statistically significant.

Biologic Plausibility: This study showed higher risk of ovarian cancer in women who had patent reproductive systems (e.g. did not have tubal ligation or fallopian tube removal or hysterectomy). This is consistent with the biology of the reproductive tract of women in which talc, as a foreign body, can be transported up through the reproductive tract to reach the fallopian tubes and ovaries (both of which can be the initial sites of ovarian cancers). That the risk in women without patent tubes was not zero could be due to talc exposure before such surgeries occurred, or to incomplete lack of patency. (Pregnancies can occur in a small percent of tubal ligation patients due to incomplete blockage of tubes for example.)(Lawrie, Kulier et al. 2016)

The American Society of Clinical Oncology, which represents almost 50,000 oncology professionals, issued a press release on this study and quoted Dr. O'Brien: "Despite challenges in assessing exposure history and biases inherent in retrospective data, our findings are robust, showing a consistent association between genital talc use and ovarian cancer," said lead study author Katie M. O'Brien, Ph.D., researcher at the Epidemiology Branch of the National Institute of Environmental Health Sciences. "This study leverages detailed lifetime exposure histories, and the unique design of the Sister Study, to provide more reliable evidence that supports a potential association between long-term and frequent genital talc use and ovarian cancer."

Other medical and research institutions and organizations that discussed the new Sister Study findings include the National Institute of Health (to which both the National Cancer Institute and the National Institute of Environmental Health Sciences belong) (https://www.niehs.nih.gov/health/topics/population/whealth accessed 5/25/24).

An accompanying editorial by Harris et al. published in the same journal noted several factors that are important to my report and this litigation (Harris, Davis et al. 2024):

1) The published cohort studies on ovarian cancer and exposure to genital talcum powder are likely to suffer from nondifferential misclassification because only limited information was obtained on use of genital talcum powder products -- "... cohort studies, which have less detailed on powder exposure (leading to nondifferential misclassification), have provided more ambiguous results, with limited power to detect modest associations even when data are pooled across studies."

2) This new O'Brien et al. publication on the Sister Study highlights the critical window of risk, as O'Brien found the highest relative risks with exposures that occurred when women were in the 20s and 30s. They state that this window of time is consistent with other risk factors which also have their greatest impact when they occur during that same window (e.g. contraception, parity, and breastfeeding).
3) These new analyses "illustrated a method for addressing the potential role of exposure misclassification when reporting results in epidemiologic studies." Harris et al. point out that even with misreporting of genital powder use in half of the cases, a significant increase in ovarian cancer risk was seen, "adding support to the plausibility of a true association between genital powder use and ovarian cancer risk."
4) The new O'Brien study addresses recall bias. As Harris et al. explain, the authors "considered a range of possible exposure misclassifications by both the cases and controls and recalculated the results to show that even with a fairly large degree of exposure misclassification the association persists (although attenuated), suggesting that this type of bias cannot fully explain the results." Further, Harris et al. state that recall bias, if in effect, should have resulted in increased relative risks for uterine cancer, and state, "the lack of an association between genital powder use and uterine cancer provides additional support that recall bias does not fully explain the genital powder and ovarian cancer association."
5) Harris et al. state that the O'Brien et al. data suggest that people at risk of ovarian cancer, particularly those in their 20s and 30s, should be made aware of the potential risks.

In summary, these new data from the National Institution of Environmental Health Sciences Sister Study shows clear evidence that genital talc exposure increases risk of ovarian cancer. Risks were high, with a doubling or more of risk with high exposure. There was clear evidence of a dose-response effect. These data from a prospective cohort study now include lifetime exposure, making it the only cohort study with such comprehensive data, and the results are consistent with case-control studies' lifetime exposure results. The increased risk with patent reproductive systems is consistent with the known biology of ovarian cancer. This study confirms my causal analysis finding from the totality of epidemiologic research that exposure to talcum powder products can cause ovarian cancer.

Women's Health Initiative

In 2014, a report on the use of perineal powder in relation to ovarian cancer risk was published, using a total of 429 cases of women with ovarian cancer from the Women's Health Initiative cohort study. (Houghton, Reeves et al. 2014) Women were aged 50-79 years at study entry, and were recruited from 40 clinical centers across the United States between 1993-1998. While over 93,000 women were enrolled in the Women's Health Initiative cohort, this analysis included only 61,576. The largest number, 20,960, were excluded because they reported previously having had both ovaries removed or did not know whether they had any ovaries at the time of enrollment. Also excluded were 10,622 women with a history of any invasive cancer at enrollment. A further 516 were missing follow-up information. At study entry, women reported use of perineal powder on self-administered standardized questionnaires, in which they were asked if they had ever used powder on their genital areas. Those who responded yes were then asked to indicate if they used them for less than 1 year, 1-4 years, 5-9 years, or 20 or more years. Women who reported ever using a diaphragm were asked if they used powder on the diaphragm, and for what duration. Women were also asked if they used powder on a sanitary napkin/pad, again with questions about duration. Because of the relatively small number of ovarian cancer cases (429) that occurred during the study, the investigators combined the duration categories into never, 9 years or less, or 10 years or more. The investigators then created one variable by combining the perineal use, diaphragm use, and sanitary napkin use, with duration as the maximum duration for any of the 3 application areas. Cases of ovarian cancer were identified by participants on annual follow-up questionnaires; no updates on talc use were included. Medical records and pathology reports were requested for each self-reported case and were adjudicated by clinic physicians and central cancer adjudicators. A total of 429 cases were included in the analysis.

Ever use of perineal powder was associated with a non-statistically significant 6% increased risk of ovarian cancer compared with never use (hazard ratio 1.06, 95% confidence interval 0.87 - 1.28). Risk of serous invasive cancer was increased by a non-statistically significant 13% (hazard ratio 1.13, 95% CI 0.84 - 1.51). Both of these results, while not statistically significant, are consistent with an association between talcum powder product use and risk of ovarian cancer overall and of serous ovarian cancer.

Nurses' Health Study

The Nurses' Health Study is a cohort established in 1976 that had 307 cases of ovarian cancer at its initial publication in 2000; further data with a total of 210 cases were published in 2008; and an unknown number of cases were analyzed for publication in 2010. The study initially enrolled 121,700 registered nurses between the ages of 30-55 years from across the United States. Use of talcum powder was ascertained on the self-administered 1982 questionnaire only, by asking women if they had ever commonly used talcum, baby powder, or deodorizing powder on their perineal areas. Possible responses were: no, daily, 1-6 times per week, or less than once per week. Women were also asked if they had applied these products to sanitary napkins. "Ever talc use" was classified as ever talc use on either the perineal area or sanitary napkins. Every two years, participants reported health updates; no updates on talc use were included, but self-reported cases of ovarian cancer were adjudicated through medical record reviews. Women were excluded from talcum powder products analyses if they did not complete the information on the 1982 questionnaire, if they reported having had both ovaries removed, if they had had a hysterectomy but did not report whether or not they had at least one ovary remaining, or if they had a history of radiation therapy.

There have been three publications from the Nurses' Health Study on the relationship between talcum powder products and risk for ovarian cancer. (Gertig, Hunter et al. 2000, Gates, Tworoger et al. 2008, Gates, Rosner et al. 2010) The first, published in 2000, included 78,630 women, of whom 307 cases of ovarian cancer were diagnosed during a 14 year follow-up period. Ever use of talc was reported by 40.4% of the cohort; 14.5% ever used talc daily. (Gertig, Hunter et al. 2000)

The risk of ovarian cancer was not statistically significantly associated with epithelial ovarian cancer overall (relative risk 1.09, 95% CI 0.86-1.37), and risk did not increase with increasing frequency of use. Risk of serous ovarian cancer, however, was statistically significantly increased by 40% in women who had ever used talc (relative risk 1.4, 95% CI 1.02-1.91).

The second report from the Nurses' Health Study was in 2008. (Gates, Tworoger et al. 2008) In this study, 210 cases and a random sample of 600 controls from the Nurses' Health Study were combined with cases and controls from other case-control studies. Among the Nurses' Health Study cases and controls, the relative risk for ovarian cancer was 1.24 (95% CI 0.83-1.83). Daily use was associated with a

44% increase in risk (relative risk 1.44, 95% CI 0.88-2.37), although neither association was statistically significant. Given that only 210 Nurses' Health Study cases were included, the lack of statistical significance is likely due to this insufficient sample size. Importantly, for the Woolen et al. meta-analysis of high-frequency exposure to talc in the genital areas, the Nurses' Health Study provided updated data on daily use after a median 33.2 years' follow-up. (O'Brien, Tworoger et al. 2020, Woolen, Lazar et al. 2022) Woolen et al. divided these Nurses' Health Study participants into never-users, daily users, and less frequent users. A total of 706 ovarian cancer cases reported no use, 216 used daily, and 302 used less frequently. Women who were daily users had a statistically significant increased risk of ovarian cancer compared with never-users (hazard ratio 1.27, 95% CI1.09-1.49). Among women with patent fallopian tubes, the risk of ovarian cancer was increased by a statistically significant 40% (hazard ratio 1.40, 95% CI 1.17-1.68). That an elevation in risk with daily use was reported with the 210 cases in the 2008 Gates et al study as seen in the 2022 publication with 1226 in the Woolen et al analysis, but only the latter was statistically significant, points to the strong influence of the number of cases on whether or not a result has a confidence interval that excludes 1.0 (a common definition of "statistical significance"). Note that the lack of "statistical significance" does not mean that a study is unreliable. Rather, it simply reflects the smaller number of cases in the first Nurses' Health Study of daily use of talc in the genital area in relation to ovarian cancer risk (see above for discussion of the American Statistical Association's perspective on "statistical significance").

The third Nurses' Health Study report was published in 2010. (Gates, Rosner et al. 2010) This report looked at multiple menstrual, hormonal, health habits, and familial risk factors for ovarian cancer; the variable on use of talc to the perineal area was limited to a dichotomous "greater than or equal to once per week vs. less than once per week)".

Use of talc one or more times per week compared with less use was not statistically significantly related to risk for epithelial ovarian cancer (relative risk 1.06, 95% CI 0.89-1.28), serous invasive (relative risk 1.06, 95% CI 0.84-1.35), or for other subtypes including endometrioid, or mucinous ovarian cancer.

It is difficult to compare the results of these three Nurses' Health Study publications. The first and third used different categories of use as the referent (comparison) group. The first publication used "never use" as the comparison and found a statistically significant effect for risk of serous ovarian cancer with any use of talcum powder products. The third publication combined "never use" and "less than once per

week" into one referent category. If low frequency use increases risk of ovarian cancer, which is entirely plausible, combining such women with never users will seriously underestimate the true relative risk associated with use of talcum powder products. The second publication found increased risks of total and serous ovarian cancer with use of talcum powder products, but the numbers were small and therefore the results were not statistically significant.

Cohort Studies Analysis

All of the three cohort studies found increases in risk of ovarian cancer overall among women who used talcum powder products in the perineal areas. The updated Sister Study, however, showed statistically significant increased risk of ovarian cancer with genital talc use when lifetime use was ascertained. This study also found strong dose-response relationships between frequency and duration of genital talc use with ovarian cancer risk, that were statistically significant. The results of the Women's Health Initiative and the Nurses' Health Study were not statistically significant for ovarian cancer overall, likely due to insufficient sample size or incomplete ascertainment of talc exposure. The first Nurses' Health Study publication found a statistically significant association between ever versus never use and risk of serous ovarian cancer. The updated Sister Study found statistically significant increased risk of serous ovarian cancers with ever use of genital talc. The first Sister Study analysis found a reduced risk of ovarian cancer but did not report data by histologic subtype of ovarian cancer. Similar to the Nurses' Health Study, the Women's Health Initiative found an increase, albeit non-statistically significant, in risk of serous ovarian cancer in users versus nonusers of talcum powder products.

There were serious limitations to these cohort study analyses. None of the studies were specifically designed to investigate the relationship of talcum powder product use and risk of ovarian cancer. Rather, the cohorts were designed to study a large number of outcomes and a wide variety of exposures. Only the Sister Study obtained detailed lifetime histories of talcum powder product use, although two did ask about duration of use for current users. Only the updated Sister Study was able to accurately measure dose of exposure. The sample sizes (numbers of cases) of the Nurses Health Study and Women's Health Initiative publications were likely too small to be able to detect a relative risk in the order of 1.24 (the value found in the Terry pooled analysis (Terry, Karageorgi et al. 2013)) with reasonable power, especially for different histologic subtypes.

To assess likelihood of inadequate sample sizes in these cohort studies, I used an online calculator: http://www.openepi.com/SampleSize/SSCohort.htm. I used WHI data (Houghton, Reeves et al. 2014) to estimate the cohort sizes needed to determine a true relative risk of 1.24 (i.e. the relative risk from Terry et al pooled analysis (Terry, Karageorgi et al. 2013)) with 50% exposure to talcum powder products in non-cases, and an assumption of 0.5% occurrence of ovarian cancer in unexposed women (Anderson, Judd et al. 2003) over 12 years' follow-up (the mean number of years of follow-up in the WHI publication). My calculations show that to have sufficient power to identify a statistically significant relative risk of 1.24, the necessary cohort size would be over 140,000. None of the 3 cohorts had this large a sample size for these publications. Sample size ultimately rests on the numbers of cases that occur, rather than the actual cohort size. While the third Nurses' Health Study publication (Gates, Rosner et al. 2010)—had a large sample size of cases, the authors' choice to combine never users with less than once per week users could have significantly attenuated the relative risk estimates.

Results of the Nurses' Health Study and Women's Health Initiative cohort studies were overall attenuated compared with results of the case-control studies. However, the trend for all of the cohort studies was a positive relative risk of talcum powder product use and risk of ovarian cancer. In the Nurses' Health Study, women who used these products had a statistically significant 40% increased risk of developing serous invasive ovarian cancer compared with non-users. (Gertig, Hunter et al. 2000) In that study, use in the perineal area directly or on sanitary napkins increased risk of ovarian cancer overall by a non-statistically significant 15%. In the Women's Health Initiative, use of talcum powder products to the genital area (or on sanitary napkins or diaphragm) increased risk overall by a non-statistically significant 6%, and risk of serous invasive ovarian cancer by a non-statistically significant 13%.

The first Sister Study asked only about use of talcum powder product use in the 12 months prior to enrollment; just 14% of the cohort used these products in that period. The cohort included only women at high risk for breast cancer recruited beginning in 2003—this may have been a group of women who were aware of the potential carcinogenic effect of talc, and therefore avoided use. The first analysis of this cohort study found a non-statistically significant 27% lower risk of developing ovarian cancer in users versus non-users. Given the likely 30-50-year latency of ovarian cancer development after exposure to a carcinogen (Purdie, Bain et al. 2003), however, these results of the Sister Study are not likely reflective of risk from exposure to talcum powder products. The updated Sister Study data, which

asked women about their lifetime use of genital talc, showed a statistically significant 40% increased risk of ovarian cancer with ever use of genital talc. This increased risk was even stronger, and was statistically significant, with the most frequent use, and the longest duration of use.

Taken together, the epidemiologic data, including cohort and case-control studies, show a remarkably consistent increase in risk of ovarian cancer with exposure to genital talcum powder products. The recall bias analyses in the Sister Study show that recall bias is unlikely to explain all of the elevation in risk seen in case-control studies. Therefore, the results bolster my confidence in the observations from the 28 case-control studies described above.

In summary, while two of the cohort studies showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, it was likely due to systematic misclassification of genital talc exposure which underestimates relative risk. (O'Brien, Wentzensen et al. 2024) The strong, consistent, and statistically significant results of the Sister Study cohort, the case-control studies, and as described below, the meta-analyses and pooled analyses support the positive association between genital talcum powder product use and risk ovarian cancer.

Meta-Analyses and Pooled Analyses

I reviewed 9 meta-analyses (Harlow, Cramer et al. 1992, Gross and Berg 1995, Cramer, Liberman et al. 1999, Huncharek, Geschwind et al. 2003, Langseth, Hankinson et al. 2008, Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020, Woolen, Lazar et al. 2022) and four pooled analyses (Terry, Karageorgi et al. 2013, O'Brien, Tworoger et al. 2020, Davis, Bandera et al. 2021, Phung, Muthukumar et al. 2022) All of the meta-analyses, and the pooled analyses, found elevated summary risks for ovarian cancer associated with use of talcum powder products. All but the pooled cohort studies' overall results' relative risks were statistically significant. Although many of the source studies from which they performed their meta-analyses had elevated risks for ovarian cancer with use of talcum powder products, the relative risks or odds ratios were not all statistically significant. I interpret the lack of statistical significance in some source studies as being due to the small sample sizes of many of these studies. I calculated the sample size required for a study in which 40% of controls used talcum powder products, in which there is good power (80%) to detect a relative risk of 1.3, and that had low chance of estimated a particular relative risk by chance

(http://www.openepi.com/SampleSize/SSCC.htm). The calculation showed that the minimum number of cases and controls would need to be 931 each, for a total sample size of 1862. Almost none of the case-control or cohort studies had sample sizes this large. Lack of statistical significance found in the various studies is likely due to their small sample sizes. For this reason, evaluation of the meta-analyses and pooled analysis, with their larger sample sizes, is critical to understanding the state of epidemiologic evidence linking use of talcum powder products to risk of ovarian cancer. Note, none of the meta-analyses or pooled analyses included the most recent, updated, data from the Sister Study.

Critical Review of the Association between Perineal Use of Talc Powder and Risk of Ovarian Cancer (Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020)

The most recent meta-analysis of the association of perineal use of talc powder and ovarian cancer risk was published by Canadian researchers in 2019 (with data published in 2020). (Kadry Taher, Farhat et al. 2019, Taher, Farhat et al. 2020) The investigators conducted a standardized systematic search and meta-analysis, following PRISMA and Cochrane systematic review guidelines. They searched multiple databases using standardized search terms for both human epidemiological studies and animal studies. Multi-level screening and text examination yielded 30 epidemiological studies for inclusion, of which 24 were case-control and 4 were cohort studies. Numbers of cases per study ranged from 46 to 2,041. The investigators evaluated study quality using the Newcastle Ottawa system.

Overall meta-analysis indicated that risk of ovarian cancer with ever use of talc in the perineal area increased ovarian cancer risk by a statistically significant 28% (odds ratio 1.28, 95% CI 1.2-1.37, $p<0.0001$). The authors state that this finding is similar to previous meta-analyses results. The authors investigated associations in subgroups for those studies with data. They found that risk was more apparent in Hispanic and White women, in those applying talc to underwear, in pre-menopausal women, in postmenopausal women on menopausal hormone therapy, and for serous and endometroid types of ovarian cancer. The odds ratios differed by mode of exposure. For application to underwear it was a statistically significant 1.7 (95% CI 1.27-2.28) and to sanitary napkins it was 1.12 (95% CI 0.91-1.39). Risk for application to diaphragms and condoms was not increased, which makes sense since women would be told to use spermicidal gel inside the diaphragm which would impede any talc remaining after dusting and rinsing before use, and talc dusting of condoms is variable by manufacturer and time.

For serous cancer, the meta-analysis odds ratio was a statistically significant 1.38 (95% CI 1.22-1.56), and for endometroid it was 1.39 (95% CI 1.09-1.82). The odds ratio for mucinous was 1.05 (95% CI 0.85-1.29), although for invasive mucinous it was 1.34 (95% CI 0.48-3.79). The authors noted low heterogeneity among studies (which points to consistency across studies). Risk estimates were higher for case-control studies (odds ratio 1.32, 95% CI 1.24-1.4) than cohort studies (odds ratio 1.06, 95% CI 0.9-1.25). There were no differences by Newcastle-Ottawa scale, showing study quality did not affect results. Nor did any one study affect results when removed from analysis.

The meta-analysis showed a dose-response effect for frequency. Low (1-<10 days/month), medium (1/day for 10-25 days/month), and high (1/day for > 25 days/month) frequency use categories yielded odds ratios of 1.22, 1.22, and 1.39 versus nonusers was found. The odds ratio for the highest frequency was statistically significant. Increased duration of use did not increase risk, however. The authors assessed a composite of frequency times duration exposure as "talc-years," and state that "Overall, the graphical results …suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc…" but state that there was a high degree of uncertainty with individual risk estimates.

The results of this 2019 meta-analysis give strong support for an association between perineal talcum powder product use and risk for ovarian cancer. A significant number of the aspects of the causal relationship that Bradford Hill describes in his address are present in these data, including strength, consistency, temporality, and biologic gradient. Bradford Hill did not define his first aspect—strength—other than to say that the likelihood of causality is greater if the agent causes a "several fold higher" increase in risk in exposed persons. The Canadian government used the results of this work in their weight-of-evidence analysis Screening Assessment on Talc, and determined that the current data on talc and ovarian cancer are indicative of a causal effect (see description of the Canada Screening Assessment on Talc later in this report).

Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-analysis (R. Penninkilampi, Eslick GD, 2018)

In this meta-analysis and systematic review, the authors searched 6 electronic databases, and selected observational studies with at least 50 cases of ovarian cancer. (Penninkilampi and Eslick 2018) They

analyzed the association between ovarian cancer, including specific sub-types, and the following variables regarding talcum powder products: any perineal talc use, long-term (> 10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. Included were 24 case-control studies, with 13,421 ovarian cancer cases. Also included were three cohort studies, with 890 cases and a comparison of 181,860 person-years [numbers of non-cases multiplied by the years of follow-up]).

The authors found that any perineal talc use was associated with a statistically significant 31% increased risk for ovarian cancer (odds ratio 1.31, 95% CI 1.24-1.39).

There was evidence of a dose-response effect by number of lifetime applications. Women whose lifetime applications totaled less than 3600 had a statistically significant 32% increased risk of developing ovarian cancer (odds ratio 1.32, 95% CI 1.15-1.50), while those whose lifetime applications totaled over 3600 had a statistically significant 42% increased risk for ovarian cancer (odds ratio 1.42, 95% CI 1.25-1.61).

Increased risks were seen for all types of ovarian cancer, as well as specific subtypes: all serous (odds ratio 1.32, 95% CI 1.22-1.43), serous invasive (odds ratio 1.32, 95% CI 1.13-1.54), serous borderline (odds ratio 1.39, 95% CI 1.09-1.78), and endometrioid (odds ratio 1.35, 95% CI 1.14-1.6). For all of these subtypes, the confidence intervals did not include 1.0, and therefore are considered statistically significant and unlikely to be due to chance findings. For other subtypes, the following non-statistically significant associations were seen: all mucinous (odds ratio 1.12), mucinous invasive (odds ratio 1.34), mucinous borderline (odds ratio 1.18), and clear cell (odds ratio 1.02).

The association between ever use of talc and overall ovarian cancer risk was higher in case-control studies (odds ratio 1.35, 95% CI 1.27-1.43) than in cohort studies (odds ratio 1.06, 95% CI 0.90-1.25). However, the results for case-control and cohort studies were similar for serous ovarian cancer. In cohort studies, risk for serous invasive cancer was statistically significantly increased by 25% with any perineal talc use (odds ratio 1.25, 95% CI 1.01-1.55), and in case-control studies, it was statistically significantly increased by 36% (odds ratio 1.05-1.75). There was insufficient information from the cohort studies to calculate the dose-response variable (total lifetime applications).

In my opinion, the results of this 2018 meta-analysis give strong support for an association between perineal talcum powder product use and risk for ovarian cancer. A significant number of the aspects of the causal relationship that Bradford Hill describes in his address are present in these data, including strength, consistency, temporality, and biologic gradient. Bradford Hill did not define his first aspect—strength—other than to say that the likelihood of causality is greater if the agent causes a "several fold higher" increase in risk in exposed persons. However, for agents like perineal talcum powder products that have such high prevalence of use (over 50% in some populations), the odds ratio/relative risk/hazard ratio for perineal talc use is of great importance for both public health and clinical medicine because it means that perineal talc use causes a significant number of ovarian cancer cases every year.

The corollary example of combined estrogen plus progesterone menopausal hormone therapy and breast cancer risk is helpful here. The Women's Health Initiative clinical trial showed that this type of hormone therapy increases risk of breast cancer by 26% after an average 5 years of use. That level of risk was sufficient for clinical interest groups and governmental agencies to advise women to use hormone therapy for limited periods of time, if at all, because of risk for breast cancer and other adverse events with similar levels of increased risk (29% increase in coronary heart disease, and 41% increase in stroke). (Rossouw, Anderson et al. 2002) Further examples of relative risks less than 1.5 that have significant public health impact because of high prevalence of exposure in the population or in specific subgroups are shown on pages 26-27.

Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis (Berge W, Mundt K, Luu H, Boffetta P, 2017)

The authors of this meta-analysis performed a systematic search of PubMed, Embase, and Scopus databases(Berge, Mundt et al. 2017). After quality assurance and redundancy checks, they included in their analysis 24 case-control studies and 3 cohort studies that reported on the association between talcum powder products and risk of developing ovarian cancer. The main meta-analysis compared ever versus never use of genital talc. Additional analyses looked at use of powder on sanitary napkins and diaphragms. Stratified analyses were conducted for tumor types.

From the meta-analysis, the authors observed a statistically significant 22% increased risk of developing ovarian cancer in women who had ever used genital talc versus never users (relative risk 1.22, 95% CI 1.13-1.30).

Significant results were found for dose-response relationships, both for number of years of use and for number of applications. Each 10-year increase in genital talc use was associated with a 16% increase in risk for developing ovarian cancer (relative risk 1.16, 95% CI 1.07-1.26). Furthermore, each increase of one application per week was associated with a 5% increase in risk (relative risk 1.05, 95% CI 1.04-1.07).

Risk of serous carcinoma was the only subtype of ovarian cancer for which risk was elevated, and it was statistically significant (relative risk 1.24, 95% CI 1.15-1.34). "Late" exposure, which the authors hypothesized could be less likely to include asbestos, conferred a higher risk (relative risk 1.31, 95% CI 1.03-1.61) than did "early" exposure (relative risk 1.18, 95% 0.99-1.37). Neither specific use on a sanitary napkin nor on a diaphragm increased risk. Ever use of genital talc on a diaphragm was associated with decreased risk (relative risk 0.75, 95% CI 0.63-0.88).

The association of talcum powder use with increased risk of ovarian cancer was seen in case-control studies (relative risk 1.26, 95% confidence interval 1.17-1.35) but not in cohort studies (relative risk 1.02, 95% confidence interval 0.85-1.2). Furthermore, hospital-based case-control studies had a higher summary relative risk compared with population-based case-control studies (relative risks 1.34 and 1.24, respectively, both statistically significant).

In my opinion, the results of this meta-analysis are very similar to those of the later ones described above, and further support the causal effect on ovarian cancer of talcum powder products applied in the perineal area.

Perineal Use of Talc and Risk of Ovarian Cancer (Langseth, Hankinson, Siemiatycki, Weiderpass, 2017)

In a meta-analysis conducted by some of the researchers who had investigated the epidemiologic research on talc exposure and ovarian cancer risk for IARC, data from 20 case-control studies were combined into a meta-analysis. (Langseth, Hankinson et al. 2008) The authors found an overall odds

ratio of 1.35 (95% CI 1.26-1.46) for ever- versus never-use of talcum powder products. The authors did not perform dose-response analyses.

Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies. (Huncharek, Geschwind, Kupelnick, 2003)

This meta-analysis included fifteen case-control and two cohort studies that had been published between 1966 and early 2001, and that fit eligibility criteria, including documenting type of talc exposure (e.g. dusting perineum vs. sanitary napkins). The meta-analysis produced a statistically significant relative risk of 1.33 (95% confidence intervals 1.16-1.45) for ever versus never use of talc in the perineal area. (Huncharek, Geschwind et al. 2003)

The investigators addressed dose-response in the seven studies with information on years of talc exposure or numbers of talc applications per month. However, the authors combined categories of dose (applications per month) and duration of use (years) into one variable, and treated the dose-response analysis as if dose and duration were measuring the same construct. Their statement of lack of dose-response effect, therefore, is misleading in my opinion. The authors suggest that perhaps talc use has a similar carcinogenic effect as asbestos, and cites research showing that asbestos does not show a clear dose-response effect on risk of mesothelioma.

The authors also separated the results of hospital-based (e.g. both cases and controls from the same hospitals) from non-hospital-based (controls selected from the general population) and found a lower relative risk for ovarian cancer (1.19, not statistically significant) for the hospital-based studies and 1.38 (statistically significant) for population-based studies. The authors state that the hospital-based studies would be more accurate because they eliminate bias from case referral patterns to particular hospitals. However, many of the non-hospital-based studies used population-based case ascertainment (e.g. cancer registries) and selected population-based controls, which also eliminates the potential bias of hospital referral patterns.

Genital Talc Exposure and Risk of Ovarian Cancer (Cramer, Liberman, Titus-Ernstoff, Welch, Greenberg, Baron, Harlow, 1999)

In a paper that presented data for a case-control study of genital talc exposure and risk of ovarian cancer, Cramer et al. presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer. (Cramer, Liberman et al. 1999) The authors included results from 14 case-control studies, from which they found a statistically significant combined odds ratio of 1.36 (95% confidence interval 1.24-1.49).

A Meta-Analytical Approach Examining the Potential Relationship between Talc Exposure and Ovarian Cancer (Gross and Berg, 1995)

In a meta-analysis sponsored by the Johnson and Johnson company, Gross and Berg included nine case-control and one cohort study in a meta-analysis, and found that the relative risk for women "exposed" versus "non-exposed" to talc was a statistically significant 1.27 (95% confidence interval 1.09-1.48). (Gross and Berg 1995) Eliminating studies that included non-epithelial ovarian tumors, and studies that did not adjust for potential confounders, the relative risk remained statistically significant (relative risk 1.29, 95% confidence interval 1.02-1.63).

Perineal Exposure to Talc and Ovarian Cancer Risk (Harlow, Cramer, Bell, Welch, 1992)

Harlow and colleagues presented results of a meta-analysis of previous publications on the relationship between talcum powder product use and risk of ovarian cancer (in the same paper in which they presented data on a case-control study of ovarian cancer risk in relation to perineal talcum powder product exposure). (Harlow, Cramer et al. 1992) The authors included results from 6 case-control studies, from which they found a statistically significant combined odds ratio of 1.3 (95% confidence interval 1.1-1.6).

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls (Terry KL *et al.*, 2013)

This pooled analysis used resources and data from the Ovarian Cancer Association Consortium, including 8 population-based case-control studies with relevant data on talcum powder product use. (Terry,

Karageorgi et al. 2013) Six of the studies were conducted in the U.S. (Cramer, Liberman et al. 1999, Pike, Pearce et al. 2004, Goodman, Lurie et al. 2008, Moorman, Palmieri et al. 2009, Rosenblatt, Weiss et al. 2011, Lo-Ciganic, Zgibor et al. 2012), one in Australia(Merritt, Green et al. 2008), and one in Canada (Chang and Risch 1997). The analysis included 8,525 cases of ovarian, fallopian tube, or peritoneal cancer and 9,859 controls selected from the general population. Five of the studies had previously reported on use of talcum powder product and risk for ovarian cancer (Chang and Risch 1997, Cramer, Liberman et al. 1999, Merritt, Green et al. 2008, Moorman, Palmieri et al. 2009, Rosenblatt, Weiss et al. 2011). To harmonize data on genital powder use across the studies, Terry *et al*. defined genital powder use as any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area. Study-specific powder questions varied in detail about type and method of application. However, the authors were able to classify women into those who "ever used" genital powders vs. those who "never used" powders in the genital area. The included studies also had extensive data on other suspected risk factors for ovarian cancer that were adjusted for in the analyses. To measure cumulative dose of genital powder use, the authors estimated lifetime number of powder applications by multiplying total months of use by frequency of use per month.

Genital powder use was reported by 25% of controls and 31% of cases. In the pooled analysis, ever use of genital powder was associated with a statistically significant 24% increased risk of ovarian cancer (odds ratio 1.24, 95% CI 1.15-1.33) versus women who never used these products. In contrast, women who had used powders only in non-genital areas had no increase in risk for ovarian cancer. Risk for several subtypes of ovarian cancer was statistically significantly increased in women who had used genital powders. Risk for invasive serous cancer was increased by 24% (1,952 cases; odds ratio 1.24, 95% CI 1.13-1.35). Risk for endometroid cancer was increased by 20% (568 cases; odds ratio 1.2, 95% CI 1.03-1.4), and risk for clear cell cancer was increased by 26% (327 cases; odds ratio 1.26, 95% CI 1.04-1.52). Risk of serous borderline cancer was increased by 45% (odds ratio 1.45, 95% CI 1.24-1.69). Risk of mucinous cell invasive cancer and mucinous cell borderline cancer were not statistically significantly associated with use of genital powder products (206 cases; odds ratios 1.06, 95% CI 0.82-1.26; and 409 cases; 1.19, 95% CI 0.98-1.43, respectively).

There was a striking similarity in findings across studies, and the statistical test for heterogeneity was not significant ($p > 0.61$). All but one study showed odds ratios greater than 1.0, of which 5 were statistically significant (i.e., the confidence intervals did not contain 1.0).

To assess dose-response effects, the authors categorized participants who had used genital powder into 4 equal groups by lowest to highest level of use (quartiles), and compared their risk for ovarian cancer to that in non-users. A clear dose-response trend was evident. Compared with never users of genital powder, women in quartile 1 had a 14% increased risk for ovarian cancer (odds ratio 1.14, 95% CI 1.00-1.31), women in quartile 2 had a 23% increased risk for ovarian cancer (odds ratio 1.23, 95% CI 1.08-1.41), women in quartile 3 had a 22% increased risk for ovarian cancer (odds ratio 1.22, 95% CI 1.07-1.40), and women in quartile 4 had a 32% increased risk for ovarian cancer (odds ratio 1.32, 95% CI 1.16-1.52). Slightly higher odds ratios were seen when the cancers were restricted to non-mucinous subtypes (i.e., serous invasive, endometroid invasive, clear cell invasive, and serous invasive): 1.18, 1.22, 1.22, and 1.37, respectively, for increasing levels of use by quartiles. When all 5 categories were included, the trend was highly statistically significant ($p_{trend} < 0.0001$).

The authors performed some additional analyses to make sure that the results were not biased. First, they excluded cases and controls who only began to use genital powders after undergoing tubal ligation or hysterectomy (after which powder likely would not migrate to the ovaries). This had no effect on the odds ratios—the increased risks for ovarian cancer remained virtually identical in each quartile. They then looked at effect of genital powder use and ovarian cancer risk by subgroups of women according to other ovarian cancer risk factors. They found no significant interactions between genital powder use and parity, reported history of endometriosis, tubal ligation/hysterectomy, or menopausal status. They did find that the effect of genital powder use was higher in normal/overweight women (odds ratio 1.28, 95% CI 1.17-1.39) than it was in women with obesity (odds ratio 1.14, 95% CI 0.98-1.32).

Finally, the authors looked at associations between genital powder use and ovarian cancer by years of beginning use. They found that the association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (odds ratio 1.36, 95% CI 1.19–1.56), between 1962 and 1972 (odds ratio 1.27, 95% CI 1.11–1.46), and after 1972 (odds ratio 1.31 95% CI 1.15–1.51). However, they observed an attenuated association for women who started genital powder use before 1952 (odds ratio 1.08, 95% CI 0.93–1.25).

The Terry *et al.* pooled analysis provides strong evidence that perineal talcum powder product use causes ovarian cancer. "Strong" here does not pertain to size of the odds ratio/relative risk. Rather, it refers to the fact that the number of cases included was larger than any previous study, the 8 case-control studies included showed similar effect sizes for association of genital powder use and ovarian cancer risk (consistency), the dose-response effect was clear, and there were enough numbers of cases to determine effects on subtypes of ovarian cancer.

Association of powder use in the genital area with risk of ovarian cancer. (Pooled analysis of four cohorts) (O'Brien, Tworoger et al. 2020)

A 2020 paper presented results of an analysis of pooled data using individual patient data from four cohort studies on the relationship between use of powder in the genital area and risk for ovarian cancer. (O'Brien, Tworoger et al. 2020) Three of the cohorts have previously published papers on this topic: Nurses' Health Study (NHS)(Gertig, Hunter et al. 2000, Gates, Tworoger et al. 2008, Gates, Rosner et al. 2010), Women's Health Initiative (WHI)(Houghton, Reeves et al. 2014), and the Sister Study (Gonzalez, O'Brien et al. 2016). The 2020 pooled study followed these three cohorts for longer periods than in their previous papers, and therefore they have included a larger number of women who had developed ovarian cancer. The pooled data consisted of 252,745 women. A total of 2168 developed ovarian cancer, of which 1884 were confirmed by medical record review. (Note, the 2024 updated Sister Study was not included in this pooled analysis.)

None of the studies updated information on exposure to talcum powder product use. The fourth cohort study, the Nurses' Health Study II (NHSII), is an offshoot of the Nurses' Health Study but collected information on powder use at a later date and used a different set of questions to ascertain powder use.

Information collected on exposure to talcum powder products varied across the cohorts. Three of the cohort studies are described above: the Nurses' Health Study, the Women's Health Initiative, and the Sister Study. The fourth, the Nurses' Health Study II, was patterned after the Nurses' Health Study, but included different aged nurses and collected data differently. In a 2013 questionnaire, the Nurses' Health Study II queried women on genital powder use: "Have you ever used talcum, baby, or deodorizing powder AT LEAST WEEKLY in the genital/rectal area or on sanitary napkins, tampons, or

underwear? Options were: never, less than 1 year, 1- < 10 years, 10-<20 years, 20-<30 years, 30+ years. Ever use therefore was defined as using at least weekly for any time period. Since the Nurses' Health Study II asked these questions only in 2013, data were missing on 41,141 cohort participants. Ever use and frequent use were both defined as using at least weekly at any time. Long-term use was defined as using at least weekly for 20 or more years.

In the pooled analysis sample, 38% reported having ever used powder in the genital area. The authors state that one purpose of the analysis was "to better examine the association between use of powder in the genital area and risk of ovarian cancer…"(1) They stated also that "…individual cohort studies are not sufficiently powered to detect modest associations, particularly if restricted to susceptible subgroups, such as women with patent reproductive tracts (i.e., having an intact uterus and no tubal ligation)'. They further state that "Because patency is required for there to be a direct physical pathway between the powder application area and the ovaries, we hypothesized *a priori* that women with patent reproductive tracts would be more susceptible to the effects of powder use in the genital area on ovarian cancer. We therefore conducted analyses restricted to this subgroup." This statement of an *a priori* hypothesis is important because it indicates that the authors realized the fact that talc moves through the reproductive tract to settle in the ovaries, fallopian tubes, and surrounding areas to cause cancer development. As described below, the data supported this hypothesis which is a key finding of this study.

The authors attempted to harmonize data on use of talcum powder products. Because the questions were asked in several ways, this meant that "ever use" was an underestimate of true ever use: 1) Nurses Health Study II participants who used less often than weekly would be classified as "never users;" 2) Sister Study participants who used between ages 14 and before 12 months prior to study enrollment, or who used after study enrollment would be classified as "never users." Nurses' Health Study participants' personal interpretation of the word "commonly" could put some actual "ever users" into the "never users" category. Women's Health Study participants who sprinkled powder on underwear but did not use directly on genital areas, diaphragms, or sanitary napkins would not have been classified as "users." All of these issues with data collection would serve to underestimate talcum powder product use and therefore underestimate the relative risks of ovarian cancer associated with use of these products. (Copeland, Checkoway et al. 1977)

Main analyses: 1) ever vs never use; 2) use in women with patent reproductive tracts

The authors calculated relative risks of the association between “ever use” and “never use” of genital powders and ovarian cancer along with 95% confidence intervals. They adjusted for several potential confounding factors: race/ethnicity, education, number of live births, ever use of oral contraceptives, history of tubal ligation, history of hysterectomy, menopausal status, and ever use of hormone therapy. They also calculated risk differences (e.g. incidence rate in women who “ever used” powder minus incidence rate in those who “never used “).

The summary relative risk (for all four cohorts together) for “ever use” vs. “never use” of powder in the genital area was 1.08 (or an 8% increased risk) with confidence intervals 0.99-1.17. A test for heterogeneity among the 4 cohorts showed low likelihood of heterogeneity. When the authors tested their *a priori* hypothesis of an elevated risk in women with patent reproductive tracts, they found a 13% increased risk of “ever use” vs. “never use”. The relative risk was 1.13 and the 95% confidence interval was 1.01-1.26. The authors interpreted this as a statistically significant finding. In a later response to comments, the authors stated that “…our results, particularly the analyses limited to women with intact reproductive tracts, should not be discounted because of lack of statistical significance… we never equated the lack of statistical significance to evidence of no association“. (O'Brien, Sandler et al. 2020) A test of heterogeneity between the four cohorts for this finding also showed low likelihood of heterogeneity.

Dose-response relationships were explored via frequency and duration, where available. Frequency of use was available for three cohorts (Nurses’ Health Study, Nurses’ Health Study II, Sister). The authors categorized women into never users, infrequent users, and use once per week or more. For all women combined, the relative risk for use at least weekly was 1.09 (95% CI 0.97-1.23). For women with patent genital tracts, however, frequent use was associated with a 19% increased risk (relative risk 1.19, 95% CI 1.03-1.37). The p test for trend was 0.03 for this latter finding, which the authors defined as statistically significant. This is highly relevant—the authors had an *a priori* hypothesis that women with patent genital tracts would have greater risk of ovarian cancer associated with genital powder use.

Length of use was available only for Nurses’ Health Study II, Women’s Health Initiative, and Sister. For Nurses’ Health Study II, long-term use was defined as use at least weekly for 20 years or more. For

Sister, long-term use was defined as using both at age 10-13 and in the 12 months prior to cohort enrollment. For Women's Health Initiative, long-term use was defined as use for 20 or more years for any of 3 categories of questions: use on private parts (genital area), use on a diaphragm, or use on a sanitary napkin or pad. The relative risk for "long-term use" in all women combined was 1.01. For women with patent reproductive tracts, the relative risk for long-term use was 1.09 (95% CI 0.97-1.23).

Additional subgroups:

The relative risks of ovarian cancer were 1.28 for race/ethnicities other than non-Hispanic whites and 1.14 for women who had ever used hormone therapy. Risk of invasive ovarian cancer was increased by 21% in women who were frequent (weekly or greater) users of genital powders (relative risk 1.21, 95% CI 1.02-1.44). The relative risk of epithelial ovarian cancer for frequent use of genital powder was 1.21 (95% CI 1.02-1.45). The relative risk for serous ovarian cancer with frequent use of genital powders was 1.18 (95% CI 0.95-1.46). Elevated relative risks for other subtypes were also seen, including endometroid, mucinous, and clear cell, all with much smaller numbers of cases and subsequently with 95% confidence intervals including 1.0. This is an issue of sample size driving the confidence intervals, rather than a finding to be dismissed.

While this pooled analysis included a larger number of cases than did the individual cohorts, the authors state in the abstract that "…the study may have been underpowered to identify a small increase in risk." In the Key Points box, they state, "…the study may have been underpowered…". In the text they state, "…individual cohort studies are not sufficiently powered to detect modest associations, particularly if restricted to susceptible subgroups, such as women with patent reproductive tracts (i.e. having an intact uterus and no tubal ligation)." In the conclusions, they state, "…the study was underpowered to detect small changes in risk," although nowhere do they define what they consider to be "small changes in risk." Further on in the discussion, they state, "…the dose-response analyses are underpowered compared with the main results and thus difficult to interpret." The concluding statement of the paper states that, "…the study may have been underpowered…". Clearly, and by the authors' own admission, several of the analyses had insufficient power to show statistical significance in the relative risks observed. Therefore, one strength of the paper is that the authors acknowledge serious deficiencies in sample size for many of the analyses.

The cohort studies all relied exclusively on self-administered forms to collect information on talcum powder product use exposure. Self-administered paper forms are the most burdensome of types of questionnaire administration (compared with in person or telephone interviews, or computer-assisted self-administered forms). (Bowling 2005) There is a resulting high potential for missing data. The cohorts included in this pooled study provided snapshots of women's exposure to genital talcum powder products. That is, none collected information on lifetime use. Global misclassification of the scale seen in this study would bias the relative risk toward the null value (that is, would reduce the relative risk closer to 1.0 than what the true relative risk actually is). (Flegal, Brownie et al. 1986)

Recent Meta-Analyses and Pooled Analyses of Genital Powder Product Use and Ovarian Cancer Risk

Since 2021, three papers in addition to the Sister Study update above have been published that provide additional analyses on associations between genital talcum powder product exposure and risk of ovarian cancer. These analyses have focused on subgroups of women (e.g. women with and without a history of endometriosis (Phung, Muthukumar et al. 2022), African-American women (Davis, Bandera et al. 2021), and women with high-frequency exposure to genital talcum powder product (Woolen, Lazar et al. 2022).

Genital Powder Use and Risk of Epithelial Ovarian Cancer in the Ovarian Cancer in Women of African Ancestry Consortium (pooled analysis of 4 case-control studies and 1 nested case-control study within a cohort, from the Ovarian Cancer in Women of African Ancestry consortium) (Davis, Bandera et al. 2021)

Investigators from the Ovarian Cancer in Women of African Ancestry Consortium analyzed data in women from four population-based case-control studies of ovarian cancer and one nested case-control study from the Women's Health Initiative cohort study. (Davis, Bandera et al. 2021) The objective of the analysis was to evaluate the association between genital powder use and epithelial ovarian cancer among African-American and White women in the consortium overall, and by histotype, and to evaluate associations between ovarian cancer risk and genital powder use by frequency and duration. To be included in the analysis, the women's interviews had to have occurred prior to 2014. (The authors state that this is "to reduce recall bias following the class action lawsuits that were filed in 2014.") Included were 620 African-American women with ovarian cancer (cases), 1146 African-American women without cancer (controls), 2800 White cases, and 6735 White controls. Women completed

questionnaires either through interview or self-administered forms. Genital powder exposure was defined as any type of powder (baby, talc, deodorizing, cornstarch, or unspecified/unknown) applied directly to the genital, perineal, or rectal area or applied indirectly on sanitary pads, tampons, or underwear. Ever use and duration of use (no use; <20 years; ≥20 years) were available for all five studies, while frequency of use (never; ≤once per week; >once per week) was available for four studies. Several risk factors were included as potential confounders, and patency of women's reproductive tracks was assessed by hysterectomy and tubal ligation status.

Ever-use of genital powder was reported in 35.8% of African-American women and 29.5% of White women. In African-American women, ever use of genital powder increased risk of ovarian cancer by 22% (odds ratio 1.22, 95% 0.97-1.53). In White women, ever use of genital powder increased risk of ovarian cancer by 36% (odds ratio 1.36, 95% 1.19-1.57). In African-American women, ever use of genital powder increased risk of high-grade serous ovarian cancer by 31% (odds ratio 1.31, 95% 1.01-1.71). In African-American women, ever use of genital powder increased risk of all other histotypes of ovarian cancer by 5% (odds ratio 1.05, 95% 0.75-1.47). In White women, ever use of genital powder increased risk of high-grade serous ovarian cancer by 33% (odds ratio 1.33, 95% 1.12-1.56). In White women, ever use of genital powder increased risk of all other histotypes of ovarian cancer by 38% (odds ratio 1.38, 95% 1.15-1.66). Similar odds ratios were observed for lower and higher frequency of use in both African-American and White women. Among all women combined, the odds ratio for long-term use (odds ratio 1.28, 95% CI 1.08-1.51) was not higher than for shorter-term use (odds ratio 1.43, 95% CI 1.22-1.68). Strengths: 1) There were relatively large numbers of African-American and White cases and controls, which increases ability to detect statistically significant associations and allows comparison of talcum powder product use and ovarian cancer risk between African-American and White women; 2) The numbers of African-American cases and controls were larger than any previous study or pooled analysis; 2) Histotype of the ovarian cancers was assessed, and numbers were sufficient to analyze data separately regarding risk of high-grade serous tumors (the most common type of epithelial ovarian cancer); 3) The case-control studies were population-based, which increases generalizability of results; 4) Genital powder exposure as well as potential confounding variables were harmonized across the five studies, which allowed for consistent adjustment for potential confounders.

Limitations: 1) Four of the studies were case-control, which have a theoretical risk of recall bias. However, the study only included women interviewed before 2014, when talc-related lawsuits were

filed, which reduces chance of bias due to cases learning of possible associations. Furthermore, the authors state: "It is likely that with the exclusion of interviews conducted in 2014 and later, any misclassification would be non-differential with respect to outcome, resulting in bias toward the null."; 2) There were some differences across studies on how genital talc use was queried. However, cases and controls from each study were asked the same questions and therefore the studies were internally consistent; 3) The investigators report that they did not observe heterogeneity across the included studies, and state that "…the results from our included prospective study (WHI) were not materially different from the 4 retrospective case-control studies."; 4) The authors state that "there was not a dose-response relationship between frequency or duration of genital powder use and ovarian cancer risk…" However, the authors chose broad dichotomies of exposure, and it is not clear if dose-response relationships would be observed with finer categorization of exposure level.

Summary: This analysis provided additional information on risk of ovarian cancer in African-American women, as well as a comparison of African-American and White women. The separate assessment for high-grade serous ovarian cancer versus all other histotypes, separately for African-American and White women provided new data for African-American women. The study adds to the already strong data showing that exposure to genital talcum powder products increases risk for ovarian cancer, and adds strength to the causality analysis on genital talcum powder product use and ovarian cancer.

Effects of Risk Factors for Ovarian Cancer in Women with and without Endometriosis (pooled analysis of 8 case-control studies in the Ovarian Cancer Association Consortium) (Phung, Muthukumar et al. 2022)

The analysis was conducted because endometriosis is a risk factor for ovarian cancer, and the authors investigated whether other ovarian cancer risk factors similarly affected women with and without a diagnosis of endometriosis. The authors state that their objective for the paper was: "To evaluate the associations between 10 well-established ovarian cancer risk factors and risk of ovarian cancer among women with vs. without endometriosis." They further state, "Our analysis considers 10 well-established ovarian cancer risk factors, including body mass index (BMI), talcum powder (i.e., talc) use, family history of ovarian cancer, nonsteroidal anti-inflammatory drug (NSAID) use, breastfeeding, hormonal oral contraceptive use, parity, tubal ligation, menopausal hormone therapy (HT) use (estrogen-only therapy and estrogen-progestin therapy), and age at menarche." The analysis included 4851 women

with ovarian cancer and 7919 control women without cancer who had complete information on talcum powder product use. The analysis limited risk factors of interest to 10: genital talcum powder, body mass index, menopausal estrogen use (with or without progestin), family history of ovarian cancer, nonsteroidal anti-inflammatory drug use, breastfeeding, hormonal oral contraceptive use, parity, tubal ligation, and age at menarche. Cases and controls had been enrolled in their original studies between 1992 and 2010. Women completed questionnaires either through interview or self-administered forms. All variables were tested as potential confounding variables. Analyses were also adjusted for age, race/ethnicity, and education. Among women with a history of endometriosis, genital talc use was positively associated with risk for ovarian cancer (odds ratio 1.38, 95% CI 1.04-1.84). Among women with no history of endometriosis, genital talc use was also positively associated with risk for ovarian cancer (odds ratio 1.12, 95% CI 1.01-1.25). In discussing the odds ratios associated with talc exposure to genital areas in women with endometriosis history, the authors state that, "…inflammation has been proposed as a possible biologic mechanism for talc's association with ovarian cancer."

Strengths: 1) There were relatively large numbers of women with a history of endometriosis, which increases ability to detect statistically significant associations and allows comparison of talcum powder product use and ovarian cancer risk between women with versus without endometriosis; 2) The numbers of cases and controls were larger than any previous analysis examining the effect modification of endometriosis , which provided higher statistical power than any previous work to examine associations of talcum powder product exposure and ovarian cancer risk in these women; 3) The case-control studies were population-based, which increases generalizability of results; 4) Genital powder exposure as well as potential confounding variables were harmonized across the studies, which allowed for consistent adjustment for potential confounders.

Limitations: 1) The studies were case-control, which have a theoretical risk of recall bias. However, the analysis only included women interviewed 1992-2010, before when talc-related lawsuits were filed, which reduces chance of bias due to cases learning on possible associations; 2) There were some differences across studies on how genital talc use was queried. However, cases and controls from each study were asked the same questions and therefore the studies were internally consistent; 3) The authors did not assess associations of genital talc use with ovarian cancer risk by amount of talc (frequency, duration, or frequency multiplied by duration); 4) The authors state that there were

insufficient numbers of participants to examine influence of endometriosis history on associations between risk factors and ovarian cancer by histotype.

Summary: This paper adds information to the literature on genital exposure to talcum powder product use and risk of ovarian cancer. It confirms the consistency of associations across groups of women between talcum powder product use and ovarian cancer risk. The analysis adds to the already strong data showing that exposure to genital talcum powder products increases risk for ovarian cancer, and adds strength to the causality analysis on genital talcum powder product use and ovarian cancer. The paper also provides strong support for inflammation as a biological mechanisms linking genital exposure to talc and risk of ovarian cancer.

Association between the Frequent Use of Perineal Talcum Powder Products and Ovarian Cancer: a Systematic Review and Meta-Analysis (10 case-control studies, 1 cohort study) (Woolen, Lazar et al. 2022)

In 2022, a systematic review and meta-analysis of observational studies was published that focused on association between frequent genital exposure to talcum powder products and risk for ovarian cancer. (Woolen, Lazar et al. 2022) The authors state that previous meta-analyses on talc exposure and ovarian cancer risk harmonized exposure across studies by focusing on “ever” versus “never” use of genital talcum powder products. They then state that “ever use is a non-specific exposure that could dilute or obscure a meaningful association as ever use would combine women with low and high exposures to talcum powder.” For this meta-analysis, the authors defined “frequent” perineal talcum powder use as at least two times per week. The meta-analysis included 66,872 women, of whom 6542 were cases of ovarian cancer. The included cohort study (Nurses’ Health Study) had not previously published data on daily exposure to talcum powder products and ovarian cancer risk, but it shared data for this meta-analysis. Data were also requested from the Sister Study but were not provided because of very small numbers of women with frequent talcum powder product exposure. Other cohort studies (Nurses’ Health Study II and Women’s Health Initiative) did not have frequency data and so were not included in this meta-analysis.

The summary pooled odds ratio assessing the association between frequent use of perineal talcum powder products and ovarian cancer was 1.47 (95% CI 1.31-1.65, $p<0.0001$). There was no significant

publication bias, and the studies were homogeneous. When examined by type of study, the summary polled odds ratio for case-control studies was 1.49 (95% CI 1.29-1.72). The odds ratio for the cohort study was 1.4 (95% CI 1.17-1.68). One of the case-control studies included other body exposures of talcum powder product use with perineal powder use. Exclusion of this study did not change results (summary odds ratio 1.44, 95% CI 1.29-1.6). When the meta-analysis was limited to 10 studies with high quality assessment on the Newcastle-Ottawa Scale, the summary odds ratio also did not change: odds ratio 1.48 (95% CI 1.31-1.69, $p<0.0001$).

Strengths: 1) The analysis focused on frequent use of perineal talcum powder products. Previous meta-analyses have focused on all use ("ever use"), which can dilute size of relative risks/odds ratios if lower-dose exposure does not raise risk to the same degree as high-level exposure; 2) The analysis compared case-control summary odds ratio (1.47) to the Nurses' Health cohort study odds ratio (1.4), which shows strong consistency between results using these two epidemiologic study methodologies. The remarkable similarity between high frequency odds ratios in the cohort and case-control studies indicates that recall bias in the case-control studies is not a likely explanation for the consistent findings of elevated risk of ovarian cancer in women exposed to talcum powder products in the perineal area; 3) The included studies were high quality, with 10 of the 11 studies having scores of 7 or more on the Newcastle-Ottawa scale; 4) The meta-analysis showed low heterogeneity among studies and low probability of publication bias.

Limitations: 1) Other cohort and case-control studies did not meet inclusion criteria because their data did not capture frequent use of perineal talcum product use; 2) Some included studies were unable to differentiate between perineal talcum powder product and cornstarch users. However, other research shows only 1-2% of perineal powder users reported using cornstarch. (Cramer, Vitonis et al. 2016)

Summary: This analysis shows strong data that women who used perineal talcum powder products two or more times per week had a statistically significant 47% increased risk of developing ovarian cancer. This information adds to the previously published literature which shows a consistent elevated risk of ovarian cancer with genital exposure to talcum powder product. It adds to the dose-response effect seen in previous studies. That is, previous meta-analyses showed that "ever use" versus "never use" increased ovarian cancer risk by 22 - 31%. (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019) The Woolen et al meta-analysis, focused on high-frequency use, found a

higher odds ratio - 47% increased risk – of ovarian cancer, which supports a dose-response effect. This study provides strong support to the causal relationship between perineal talcum powder product use and risk of ovarian cancer by providing focused analyses on frequent use of these products and risk for ovarian cancer.

Summary of Meta-analyses/Pooled Analysis Results

All of the meta-analyses and the pooled analyses demonstrate increased risk of ovarian cancer in women who used talcum powder products in the genital or perineal area compared with nonusers. The earlier meta-analyses included fewer studies, primarily case-control studies. The most recent meta-analyses included three cohort studies and 24 case-control studies. (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019) The summary relative risks were quite consistent across the meta-analyses and the pooled analysis, ranging from 1.22 to 1.4 for any versus no use of perineal talcum powder products. The pooled cohort analysis found that among women with patent reproductive tracts, the relative risk for ovarian cancer was 1.13. while the overall relative risk was 1.08. (O'Brien, Tworoger et al. 2020) Furthermore, all but one of the summary results were statistically significant. Importantly, the later meta-analyses (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019) and the case-control pooled analysis (Terry, Karageorgi et al. 2013) assessed dose-response relationships, while earlier meta-analyses did not (Harlow, Cramer et al. 1992, Cramer, Liberman et al. 1999, Langseth, Hankinson et al. 2008), or did so inaccurately (Huncharek, Geschwind et al. 2003).

The newer pooled analyses and meta-analysis confirmed the earlier publication results. The Davis et al. pooled analysis confirmed that the associations between perineal talcum powder product use and ovarian cancer risk are present for African-American as well as White women. (Davis, Bandera et al. 2021) The Phung et al. pooled analysis confirms the association between talcum powder product use and ovarian cancer holds both for women with and without a history of endometriosis (another ovarian cancer risk factor). (Phung, Muthukumar et al. 2022) The Woolen et al. meta-analysis confirms the dose-response effect of talcum powder product use and ovarian cancer risk, as it shows strong and consistent associations of frequent exposure and risk. (Woolen, Lazar et al. 2022)

These findings of increased risk of ovarian cancer with perineal exposure to talcum powder products show that the observed associations overall and those for dose-response are robust.

One striking observation across the meta-analyses and pooled analysis is that the total sample sizes (numbers of cases) in all of the meta-analyses and the pooled analyses were sufficient to detect statistically significant relative risks of 1.3 for an overall "exposed" versus "non-exposed" variable with prevalence of 40 percent (see page 48 for a calculation of needed sample size). As shown in Tables 3 and 4, the numbers of cases in the meta-analyses and pooled analysis ranged from 1106 to 16,005, with controls of equal or greater number. All of these, therefore, exceed the sample size I estimated that is needed to have statistical power to determine relative risks of 1.3. In contrast, many of the individual case-control or cohort studies did not have large enough samples of cases to have statistical power to determine a relative risk of 1.3.

Summary data from the reviewed meta-analyses of risk of ovarian cancer associated with talc exposure to perineal areas are presented in Figure 1 at the end of this report. For each meta-analysis or pooled analysis publication, the following data are provided: number of studies included, number of cases in total, whether a dose-response (DR) analysis was conducted and the result, the relative risk (RR) (here used as a term for any of relative risk, odds ratio, or hazard ratio), lower limit of confidence interval (CIL), and upper limit of confidence interval (UIL). The graph shows, for each study, the relative risk for "ever" versus "never" exposure to perineal talc, depicted by filled-in squares. The bar lines around the square represent the upper and lower confidence intervals around the respective relative risk.

Data from individual case-control and cohort studies are presented in Figure 2 at the end of this report. For each study publication, the following data are provided: number of cases in total, number of controls (case-control studies), number of non-cases (cohort studies), whether population-based or hospital-based (case-control studies), length of follow-up (cohort studies), whether a dose-response (DR) analysis was conducted and the result, the relative risk (RR) (here used as a term for any of relative risk, odds ratio, or hazard ratio), lower limit of confidence interval (CIL), and upper limit of confidence interval (UIL). The graph shows, for each study, the relative risk for "ever" versus "never" exposure to perineal talc, depicted by filled-in squares. The bar lines around the square represent the upper and lower confidence intervals around the respective relative risk.

Other Reviews of Talcum Powder Product Exposure and Ovarian Cancer Risk

Some systematic reviews on talc exposure and ovarian cancer risk have been published. (Wentzensen and O'Brien 2021) (Goodman, Kerper et al. 2020, Lynch, Lauer et al. 2023) as well as one umbrella study of systematic reviews/meta-analyses of multiple ovarian cancer risk factors. (Tanha, Mottaghi et al. 2021) However, these other reviews did not present summarized data such as were presented in the several comprehensive and focused meta-analyses, and therefore they did not add to my causal analysis.

Asbestos, Fibrous Talc, and Heavy Metals in Talcum Powder Products

It is important to note that talc is not asbestos-free. Talcum powder products contain other, potentially carcinogenic substances; of greatest concern is the presence of asbestos in talc, and the presence of talc with asbestiform fibers (fibrous talc), in these products. The presence of any one of these constituents add to evidence of biologic plausibility that would support the consistent increased risk seen in the epidemiologic studies.

In December 2021, the U.S. FDA published a white paper on the U.S. Interagency Working Group on Asbestos in Consumer Products (IWGACP) entitled "IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc." (https://www.regulations.gov/document/FDA-2020-N-0025-0053 accessed 11/12/23) Talc is specified in the report as "including talc intended for use in cosmetics." The report states that "Some talc deposits may also contain asbestos…", that "asbestos is a known human carcinogen" (citing IARC, U.S. EPA, and U.S. National Toxicology Program 14th Report on Carcinogens.") Importantly, the report notes that "recent testing of cosmetics by a private laboratory under contract with FDA using transmission electron microscopy revealed the presence of asbestos in samples that had negative findings for the same products using PLM, highlighting the shortcomings of optical microscopy methods." The report also states that "Exposure to asbestos may also lead to diseases in other parts of the body that are remote from the sites of primary exposure, including cancers of the larynx, gastrointestinal tract, and ovaries."

Asbestos can take several forms. Proven carcinogenic forms include serpentine (chrysotile) and amphibole (actinolite, amosite, anthophyllite, crocidolite, and tremolite) minerals. IARC(2012) Both

serpentine and amphibole asbestos forms are classified by IARC as Class 1 carcinogens. In their 2012 report, IARC stated that talc deposits may include tremolite, anthophyllite, and actinolite forms of asbestos.

Talc may form true mineral fibers that are asbestiform in habit. This form of talc is also referred to as fibrous talc and classified by IARC as a Class 1 human carcinogen. The IARC report also noted that "talc containing asbestiform fibers" is not the same as "talc contaminated by asbestos". IARC (2012) The conclusions reached in the 100c monograph about asbestos apply to fibrous talc. IARC has classified platy (non-fibrous) talc as a 2B "possible" carcinogen IARC (2010).

The primary route of exposure to asbestos is respiratory in the general population, although exposure through drinking water and exposure to hair or clothing of asbestos workers has also occurred. IARC (2012) For talc, the primary exposures listed by the IARC report are respiratory and perineal. IARC (2012)

Asbestos has been established as a cause of several types of cancer including epithelial ovarian cancer. In order to assess the causal relationship between asbestos and ovarian cancer, I conducted a literature search. My search yielded a total of 30 studies that have investigated the epidemiology of asbestos exposure and risk of ovarian cancer. Three of these were meta-analyses: two published in 2011 (Camargo, Stayner et al. 2011, Reid, de Klerk et al. 2011) and one published in 2021 described below (Nowak, Schmalfeldt et al. 2021). Several were s pooled analyses of cohorts with high asbestos exposure. (Ferrante, Chellini et al. 2017) and additional studies presented below. In addition, IARC published monographs on the carcinogenic role of asbestos, and conducted a systematic review through 2009 of asbestos and risk of ovarian cancer. IARC (1987, Straif, Benbrahim-Tallaa et al. 2009, 2012) IARC concluded that asbestos, fibrous talc, chromium, and nickel are Group 1 human carcinogens. IARC (2012) IARC also classified cobalt as a 2B "possible" carcinogen.

Asbestos Exposure and Ovarian Cancer – a Gynaecological Occupational Disease. Background, Mandatory Notification, Practical Approach. (Nowak, Schmalfeldt et al. 2021)

A 2021 report and meta-analysis from Germany stated that in 2017, ovarian cancer due to asbestos exposure was designated a new, and thereby the first, gynecological occupational disease in Germany. (Nowak, Schmalfeldt et al. 2021) In their consideration, the authors considered systematic reviews from

IARC, the meta-analyses by Camargo (Camargo, Stayner et al. 2011), Reid (Reid, de Klerk et al. 2011), and Bounin (Bounin, Charbotel et al. 2014). In addition, they expanded the Camargo meta-analysis with new study data from studies published prior to 9/16. (Langseth and Kjaerheim 2004, Ferrante, Bertolotti et al. 2007, Wang, Lin et al. 2013, Oddone, Ferrante et al. 2014, Pira, Romano et al. 2016, Oddone, Ferrante et al. 2017)

With the new studies included, the authors calculated a standardized mortality ratio (similar to relative risk) of 1.88 (95% CI 1.47-2.39). This states that there is close to a doubling - an 88% higher chance - of dying of ovarian cancer in persons with occupational asbestos exposure compared to the general populations.

The authors describe how asbestos fibers can be inhaled and reach distant organs to induce carcinogenesis: “Inhaled asbestos fibres have proven fibrogenic effects in humans as well as local tumourigenic characteristics. The carcinogenicity for the target organs lungs, larynx, pleura including pericardium, and peritoneum including tunica vaginalis testis has been clearly established for many years. IARC(2012) It is only in the last few years that the data have become more conclusive to the effect that ovarian cancer is also caused by asbestos. (Camargo, Stayner et al. 2011) Asbestos fibres are primarily inhaled with the air we breathe. Mucociliary clearance transports most of the deposited fibres first into the gastrointestinal tract and parts of it from there apparently into the abdominal cavity. In addition, lymphogenic and haematogenic transport as well as the penetration of asbestos fibres into the serous cavities of the chest and abdominal cavity are under discussion. The body’s own defensive reaction of coating the incorporated fibres with ferroproteins sometimes leads to the formation of asbestos bodies. (Grossgarten and Woitowitz 1991) These can be detected not only in the lungs but also in numerous extrapulmonary and extrathoracic organs. (Marten, Dirksen et al. 1989)”

The authors state the following with regard to causality: “It is only in the last few years that the data have become more conclusive to the effect that ovarian cancer is also caused by asbestos. (Camargo, Stayner et al. 2011)”

Strengths: 1) This is the most up-to-date paper that includes a meta-analysis of studies on occupational asbestos exposure and risk for ovarian cancer; 2) The paper was produced as part of a German government evaluation of inclusion of ovarian cancer among other asbestos-related cancers; 3) The

paper discusses how asbestos fibers can migrate through the body to induce carcinogenesis. Of particular interest is their statement on inhaled asbestos reaching the peritoneum in men including tunica vaginalis testis, which is the membrane surrounding the testes and a site of testicular cancer because this supports additional routes for asbestos to reach intra-peritoneal organs including fallopian tubes and ovaries; 4) The paper discusses causality of ovarian cancer in women exposed to asbestos.

Limitations: 1) The authors provide only brief information on their statistical analyses for the meta-analyses presented in the figure in the paper; 2) The review only includes studies to 9/16.

Summary: This study provides information through 9/2016 from additional studies on the association between asbestos exposure and risk for ovarian cancer. This adds to the causal analysis of talcum powder product use and ovarian cancer risk, because of the established asbestos content in talc products. This adds to the biological mechanisms aspects of a causal analysis, since asbestos is a known carcinogen, including ovarian cancer, with proven carcinogenic effects.

Following the Nowak et al. cut-off date of studies published through 2016, several additional publications have presented updates of cohorts of individuals exposed to asbestos. In a pooled analysis of 21 asbestos cement cohorts in Italy, the standardized mortality ratio for ovarian cancer was 2.40 (95% CI 1.28-4.1) for the highest exposure class (>6200 ff/ml-year). (Luberto, Ferrante et al. 2019) In an Italian pooled study of asbestos workers cohorts, 5741 women were included, in whom there were 43 observed ovarian cancer deaths versus 31.1 expected from population rates. This yielded a standardized mortality ratio of 1.38 (95% CI 1.0-187). (Magnani, Silvestri et al. 2020) In a more recent study, 6346 women asbestos workers were followed for cancer mortality. (Ferrante, Angelini et al. 2023) The ovarian cancer standardized mortality ratio 1.42, (95% CI 1.08-1.84).

Published data as recently as 2014 have shown that present-day talcum powder products include several types of asbestos. (Blount 1991, Gordon, Fitzgerald et al. 2014) Company documents and testimony also provide further evidence of the presence of asbestos, fibrous talc, and heavy metals in talcum powder products. (Pier) {Pier, #6;Hopkins, 2018 #7} Dr. William Longo tested historical samples provided in litigation. Test results reveal the presence of asbestos in approximately half of the samples tested. Additionally, fibrous talc was found at varying levels in all samples. {Longo, 2017 #8;Longo, 2017 #9;Longo, 2017 #10;Longo, 2018 #11;Longo, 2018 #12}

Finally, I have reviewed the report of Dr. Michael Crowley that discusses the different chemicals added to the fragrance constituents contained in Johnson's Baby Powder and Shower to Shower products. (Crowley 2018) Based on his review, he has concluded that these chemicals may contribute to the potential carcinogenicity of talcum powder products.

Therefore, based on the scientific literature and testing results, it is my opinion that the presence of asbestos, heavy metals, fibrous talc, and fragrances are all biologically plausible explanations for talcum powder products causing ovarian cancer.

Biological Mechanisms

Evidence of Migration of Talcum Powder Products (Talc, Asbestos, Other Minerals) to the Ovary and Fallopian Tubes

Clinical and laboratory studies have shown that talcum powder products can migrate to the ovaries and fallopian tubes. An early surgical study in healthy premenopausal women found that inert particles placed in women's vaginas moved to their fallopian tubes within 30 minutes in two of the three patients studied. (Egli and Newton 1961) Henderson et al. found talc particles in 10 of 13 (75%) of ovarian tumors studied using an extraction-replication technique. (Henderson, Joslin et al. 1971) The findings were replicated 8 years later, with all surgeons removing the ovaries wearing gloves with no talc, to ensure that surgical contamination was not the cause of the observed talc within ovaries. (Henderson, Hamilton et al. 1979) This replication study found talc in all 9 samples studied—3 normal ovaries, 3 cystic ovaries, and 3 adenocarcinomas.

In another relevant clinical experiment regarding migration, the researchers placed 3 ml of ^{90m}Tc-labelled human albumin microspheres in women's vaginas one day before pelvic surgery. (Venter and Iturralde 1979) Of the 21 women for whom the materials moved up from the cervical area, ovaries and fallopian tubes could be counted separate from the uterus in 14. Of these 14, 9 showed radioactivity in the fallopian tubes and ovaries, and 5 showed no radioactivity. In a pathological study as part of a case-control study of benign ovarian conditions, ovaries from 24 women were tested for presence of talc and asbestos by both electron microscopy and light microscopy. (Heller, Westhoff et al. 1996) All tested

ovaries were found to have talc present. Only half of the 24 women reported a history of perineal talc exposure, which suggests additional routes of exposure to talc, such as inhaled powder. The presence of talc was not due to surgical gloves as all surgeons wore talc-free gloves in this study. In another study employing microscopy (Raman), the study authors found talc particles in ovarian tissue samples from a woman with known perineal talc exposure that were not visible with other methods. (Campion, Smith et al. 2018)

Another study demonstrated migration of talc evaluated powder on medical gloves used to perform pelvic examinations (with gloved hand inserted into the vagina). (Sjosten, Ellis et al. 2004) This study detected powder in the peritoneal fluid, fallopian tubes, and ovaries the following day after the pelvic examination in women exposed to powdered gloves but almost none in women exposed to unpowdered gloves. The differences between the two groups were statistically significant.

In 2007, Cramer described the presence of talc particles observed in a pelvic lymph node of a 68 year old woman with stage III serous ovarian carcinoma. (Cramer, Welch et al. 2007) The authors used scanning electron microscopy to identify plate-like particulates in the 5-10 µm range within the lymph node, and energy dispersive X-ray spectroscopy revealed a magnesium and silicate signature compatible with talc. The authors also noted that talc could migrate through transport of the lymphatic system.

The results of these studies demonstrate talcum powder products can migrate from the perineal area to the ovaries and fallopian tube through both genital tract migration and inhalation. In my opinion it is biologically plausible that talcum powder products can reach the ovaries via migration from the perineum and via inhalation into the lungs, blood stream, and lymphatic system.

Inflammation in the Causal Pathway between Talcum Powder Product Use and Ovarian Cancer Development

The literature suggests that a likely pathway through which use of talcum powder products increases risk of ovarian cancer is through talc-induced inflammatory response. (Maccio and Madeddu 2012) As described above, it is well supported that talc can migrate through the female genital tract and settle in the area of the ovaries, fallopian tubes, and peritoneum (Henderson, Joslin et al. 1971, Henderson, Hamilton et al. 1979, Longo and Young 1979, Venter and Iturralde 1979, Heller, Westhoff et al. 1996,

Cramer, Welch et al. 2007). Increased blood levels of biomarkers of inflammation have been linked to increased risk for ovarian cancer. A recent meta-analysis of 8 cohort studies found that women with high blood levels of c-reactive protein (a marker of increased systemic inflammation) had almost double the risk of developing ovarian cancer compared with women with low levels.
(Zeng, Wei et al. 2016)

Further evidence of the inflammation mechanism comes from studies which evaluate anti-inflammatories, like aspirin and NSAIDs, and reduction of risk of ovarian cancer. A pooled analysis of case-control studies published in 2014 showed that long-term daily use of aspirin (which blocks inflammation) decreased risk of ovarian cancer (odds ratio = 0.91; 95% CI = 0.84-0.99) Similar, but not statistically significant, results were shown for use of other nonsteroidal anti-inflammatory medications. (Trabert, Ness et al. 2014) A 2018 meta-analysis found an 11% reduced risk of ovarian cancer with aspirin use (relative risk 0.89, 95% CI 0.83-0.95). (Qiao, Yang et al. 2018) Aspirin and other nonsteroidal anti-inflammatory medications inhibit the inflammation-mediating enzyme, COX-1(Trabert, Ness et al. 2014); COX-1 is frequently overexpressed in ovarian cancer tissue. (Khunnarong, Tangjitgamol et al. 2010, Wilson, Fadare et al. 2015)

Chronic inflammation may result in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis. (Maccio and Madeddu 2012) Factors related to the inflammation of the ovarian surface and tubal epithelium, such as incessant ovulation, endometriosis, and pelvic inflammatory disease, provide further evidence of inflammation and ovarian carcinogenicity. (Pearce, Templeman et al. 2012, Rasmussen, Kjaer et al. 2017, Reid, Permuth et al. 2017)

Talc exposure has also been linked to increased inflammation. It can induce granulomas and other inflammatory responses in vivo. (Harlow and Hartge 1995, Keskin, Teksen et al. 2009) Injected into the pleural cavity to treat pneumothorax, talc stimulates an intra-pleural inflammatory reaction that causes pleural fibrosis and scarring, leading to obliteration of the pleural space and prevention of recurrent pneumothoraces. (Caesar, Jordan et al. 2017) In humans, elevated interleukin 8 (a chemotactic cytokine) occurs after pleural injection of talc . (van den Heuvel, Smit et al. 1998) In a study of over 227 patients treated with talc pleurodesis; about half received small particle talc, and half received large-particle talc. Patients who received small particle talc had significantly higher proinflammatory cytokines, particularly interleukin 8, in pleural fluid and serum after talc application. (Arellano-Orden, Romero-Falcon et al.

2013) In animal models, injection of talc into the pleura can cause local and systemic inflammatory responses {Genofre, 2009 #18} including elevated inflammation-related biomarkers c-reactive protein and interleukin 8 (Rossi, Vargas et al. 2010) as well as VEGF, and TGF-beta. (Acencio, Vargas et al. 2007) This type of inflammation can induce neoplastic changes. (Buz'Zard and Lau 2007)

Other authors identify inflammation as a likely mechanism linking genital talc exposure to ovarian cancer risk. Phung et al. explain that endometriosis is an established risk factor for ovarian cancer. Endometriosis is an inflammatory disease, inflammation plays a role in ovarian cancer development, and inflammation is a possible biological mechanism for talc's association with ovarian cancer. In additional support of this mechanistic pathway, an analysis of Brieger et al included talc exposure in an inflammation-related risk score composed of established risk factors for ovarian cancer, and compared the score to survival in ovarian cancer patients. (Brieger, Phung et al. 2022)

Additional Evidence of Biological Mechanisms

Exposing human ovarian stromal and epithelial cells to talc resulted in increases reactive oxygen species (oxidative stress), cell proliferation and neoplastic transformation of cells. (Buz'Zard and Lau 2007) Similarly, in a recent *in vitro* study by Fletcher et al., talc was applied in different concentrations, for varying numbers of hours, to epithelial ovarian cancer cell lines and normal ovarian epithelial cells. (Fletcher, Harper et al. 2019) As early as 24 hours post-treatment, they found increases in mRNA (gene expression) of pro-oxidant enzymes iNOS and MPO in talc-treated epithelial ovarian cancer cells and normal ovarian cells, compared with non-treated controls. Marked decreases in several antioxidant enzymes in talc-treated cells were also seen. This study supports the role of talc in inducing oxidative stress, providing a molecular basis for epidemiologic studies demonstrating an increased risk of ovarian cancer with perineal talcum powder product exposure. (Saed, Diamond et al. 2017) In addition, Fletcher et al. also found that talc induced a biological effect by enhancing CA-125 in ovarian cancer cells and in normal cells. (Fletcher, Harper et al. 2019) A recent study found that talcum powder induced malignant transformation in normal human primary ovarian epithelial cells, in a dose-dependent manner. (Harper, Wang et al. 2023) The result was specific to normal ovarian cells, as there was no effect on normal peritoneal fibroblasts. Furthermore, talcum powder treatment increased expression of Ki67 (a marker of proliferation) as well as p53 mutant type. Other researchers have exposed epithelial ovarian cells to talc and have found similar results. (Mandarino, Gregory et al. 2020, Emi, Rivera et al. 2021)

Talc application to human mesothelial cells in cell culture has also been shown to increase gene expression in 30 genes that are relevant to carcinogenesis, and asbestos application increased gene expression in over 200 genes. (Shukla, MacPherson et al. 2009) In the same study, asbestos application to human ovarian epithelial cells increased gene expression in two genes at 8 hours and 16 genes at 24 hours. Many of the expressed genes are relevant to the carcinogenic process. Results from this experimental study show that talc causes a statistically significant increase in gene expression in mesothelial cells in several genes related to carcinogenesis, including activating transcription factor 3 (ATF3), which controls production of several markers of inflammation. (Shukla, MacPherson et al. 2009)

Asbestos, which has been found in talcum powder products, has been classified by IARC as a known ovarian carcinogen after a systematic review of the epidemiologic and biological science. IARC(2012) Meta-analyses and one pooled analysis have addressed the association between asbestos exposure and risk of ovarian cancer. (Camargo, Stayner et al. 2011, Reid, de Klerk et al. 2011, Ferrante, Chellini et al. 2017, Nowak, Schmalfeldt et al. 2021) The studies of asbestos and ovarian cancer were typically studies of cohorts with high levels of occupational or home asbestos exposure, and comparisons were made to the general population as controls. One meta-analysis found that women exposed to asbestos had a relative risk dying of ovarian cancer of 1.77 (95% CI 1.37-2.28) compared with unexposed populations (Camargo, Stayner et al. 2011). Another meta-analysis found that women exposed to asbestos had a relative risk of developing or dying of ovarian cancer of 1.75 (95% CI 1.45-2.10) compared with unexposed women (Reid, de Klerk et al. 2011). Nowak et al conducted a meta-analysis of studies of asbestos-exposed women, and found a standardized mortality ratio of 1.88 (95% CI 1.47-2.39) for ovarian cancer deaths in women with asbestos exposure at work. (Nowak, Schmalfeldt et al. 2021) This states that there is close to a doubling - an 88% higher chance - of dying of ovarian cancer in persons with occupational asbestos exposure compared to the general populations. Additional cohort studies (Reid, Franklin et al. 2013, Wang, Lin et al. 2013, Pira, Romano et al. 2016, Ferrante, Chellini et al. 2017, Oddone, Ferrante et al. 2017) , which were published after the date of the most recent meta-analyses (Camargo, Stayner et al. 2011, Nowak, Schmalfeldt et al. 2021), as well as the pooled analyses (Ferrante, Chellini et al. 2017, Luberto, Ferrante et al. 2019, Magnani, Silvestri et al. 2020, Ferrante, Angelini et al. 2023) found similar elevated risks of ovarian cancer in women with asbestos exposure. In a pooled analysis of 21 asbestos cement cohorts in Italy, the standardized mortality ratio for ovarian cancer was 2.40 (95% CI 1.28-4.1) for the highest exposure class (>6200 ff/ml-year). (Luberto, Ferrante et al. 2019)

IARC also lists mechanisms through which asbestos can cause cancer including: impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, and resistance to apoptosis. (Straif, Benbrahim-Tallaa et al. 2009) Asbestos is another biologically plausible explanation for talcum powder products causing ovarian cancer.

It is my opinion, based on these studies, that talc and asbestos induce inflammation which results in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis. This adds to the weight of evidence and provides a plausible biological explanation for the association between genital talcum powder product use and ovarian cancer.

Another line of experiments in support of the biologically plausible mechanism for talcum powder products causing ovarian cancer were conducted in animals. A study with female rats showed that talc is absorbed through the pleural surface and rapidly disseminated throughout internal organs and lymph nodes. (Werebe, Pazetti et al. 1999) Henderson et al found that talc placed in the uteruses or vaginas of female rats moved to the animals' ovaries by four days post-administration. (Henderson, Hamilton et al. 1986)

In another study, exposure of rat ovaries to talc led to cyst formation and epithelial changes. (Hamilton, Fox et al. 1984) A methodology study discovered that talc caused superoxide anion generation and release from mouse macrophages. (Van Dyke, Patel et al. 2003)

Animal experiments conducted by the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services are highly relevant to the role of talc in carcinogenesis. An NTP rat study provided important "signal " information of talc toxicity relevant to talc and development of ovarian cancer. (1993) In an inhalation study, male and female F344/N rats were exposed to daily talc aerosols of non-asbestiform talc, with appropriate controls. NTP concluded that there was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung, and benign and malignant pheochromocytoma of the adrenal gland. The NTP also concluded that there was some evidence of

carcinogenic activity of talc in male F344 /N rats based on an increased incidence of benign and malignant pheochromocytoma of the adrenal gland.

In my opinion, these animal studies further demonstrate that talcum powder products and its attendant inflammation can induce carcinogenesis. This provides further evidence of a biologically plausible mechanism supporting causation of ovarian cancer from the use of talcum powder products.

Systematic Reviews by Governmental and Inter-governmental Organizations

Canada Screening Assessment on Talc

In 2021, Health Canada, department of the Canadian government, published its final screening assessment on talc. (HealthCanada 2021) The screening assessment was conducted by the Minister of the Environment and the Minister of Health. They considered talc's chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. The data were identified up to October 2020. The assessment focused on health effects associated with cosmetic- and pharmaceutical-grade talc, and not on potential carcinogenic constituents including asbestos.

The assessment considered toxicokinetics (routes of exposure in humans) and determined that perineal application of talc results in migration to ovaries and fallopian tubes. They reviewed the epidemiologic data on talcum powder product use and risk of ovarian cancer, including case-control, cohort, pooled, and meta-analysis studies. The studies reviewed largely mirrored those included in this report. They also reviewed animal studies and human pathological studies to evaluate biological plausibility. They then conducted a causal analysis, similar to mine, based on the Bradford-Hill considerations. (Hill 1965) This included evaluating strength of association, consistence, biological gradient (dose-response), biological plausibility, bias and confounding. Finally, they examined the weight of evidence on the causal association between talc and ovarian cancer.

After considering all data, and weighing the available lines of evidence, Health Canada's assessment concluded that the current data on talc and ovarian cancer are indicative of a causal effect. It further

concluded that talc meets criteria under Canadian law that talc constitutes or may constitute a danger in Canada to human life or health.

International Agency for Research on Cancer (IARC)

IARC is part of the World Health Organization, and has a focus on identifying the causes of cancer through its own research and by convening expert working groups and producing scientific reports. In several reports, IARC has reviewed the health effects of talc and its constituents. IARC {, 2012 #53724;IARCtalc, 2010 #44414;IARC, 1987 #1;, 1987 #43799}

In 2006, IARC convened an expert working group to evaluate the carcinogenicity of several agents including carbon black, titanium dioxide, and talc, by reviewing the scientific literature to that date. The report of that working group was published in the IARC Monograph 93 in 2010 (IARCtalc 2010) The aim was to review talc without asbestiform fibers, as that had been covered in a previous Monograph supplement in which talc with asbestiform fibers was classified as Group 1 "carcinogenic to humans." IARC(1987) From the studies that had been published up through 2006, the working group determined that perineal use of talc-based body powder is possibly carcinogenic to humans (Group 2B carcinogen). After completion of the working group evaluation, a subset of members published a review in 2008 of epidemiologic studies on genital exposure to talcum powder products and ovarian cancer risk. (Langseth, Hankinson et al. 2008) These authors concluded that, on balance, the epidemiologic evidence suggested that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk.

In 2012, IARC published a report of an expert working group that reviewed the scientific literature on several agents to determine their carcinogenicity. This was done as part of the IARC Monographs, the ongoing work of IARC to determine the carcinogenicity of agents with which humans come in contact. The group of agents reviewed for this Monograph (numbered 100C) was: arsenic, metal, fibers (including asbestos), and dust. In this report, IARC classified asbestos as a Group 1 "carcinogenic to humans." The Monograph stated (page 256): "The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established…".

Given the considerable number of individual, pooled, and meta-analytic studies published subsequent to the 2008 Monograph, IARC has determined that the re-review of carcinogenicity of domestic talc

products is high priority and has scheduled a comprehensive review in 2024. IARC(2019) (https://monographs.iarc.who.int/iarc-monographs-volume-136/ accessed 11/14/23).

The epidemiologic studies reviewed in these IARC reports are included in the present expert report.

Summary of Findings: Weight of the Evidence/Bradford Hill Analysis

The summary relative risk estimates from the most recent meta-analyses (Berge, Mundt et al. 2017, Penninkilampi and Eslick 2018, Kadry Taher, Farhat et al. 2019) and the pooled analysis (Terry, Karageorgi et al. 2013) indicate that women who have ever used talcum powder products in the perineal/genital areas have approximately 22-31% increased risk of developing ovarian cancer compared with never-users. Additional analyses from a meta-analysis focused on high-frequency exposure (2 or more times/week) to talcum powder products in the genital areas found a 47% increased risk of ovarian cancer (odds ratio 1.47, 95% CI 1.31-1.65, p<0.0001). (Woolen, Lazar et al. 2022)

This review of the association between talcum powder products in the perineal/genital area produced several clear findings. Below, they are outlined according to the aspects of causality as described by Bradford Hill. (Hill 1965) The epidemiologic evidence in total, along with the biological and pathological evidence, fits virtually all of the Bradford Hill aspects for causation, namely: the strength of the association, consistency across populations, specificity, temporality, biologic gradient (dose-response), plausibility, coherence, experiment, and analogy.

Strength of the association and statistical significance: The meta-analyses and pooled analysis showed that risk of ovarian cancer among ever users of talcum powder products is 22-31% higher than in women who never used these products. A total of 28 case-control studies, 3 prospective cohort studies, 4 meta-analyses, and 4 pooled analyses were reviewed in depth. The most recent meta-analysis found a statistically significant 38% increased risk of developing serous ovarian cancer (odds ratio 1.38, 95% CI 1.22-1.56) (Kadry Taher, Farhat et al. 2019)—representing 52% of epithelial ovarian cancer cases (Torre, Trabert et al. 2018) —in women who had ever used talcum powder products compared with never-users. The pooled case-control analysis, which included data from 5 previously published and 3 unpublished case-control studies, found similar statistically significant increased risks for overall

epithelial ovarian cancer and serous ovarian cancer (24% and 20%, respectively). The pooled cohort study found a 13% increased risk for ovarian cancer with talcum powder product use in women with patent genital tracts. The recent Woolen et al. analysis found a statistically significant 47 % increased risk for ovarian cancer with frequent use of talcum powder products to the genital areas. Thus, when combining these studies through meta-analyses, the totality of the evidence shows a statistically significant increased risk of ovarian cancer with use of perineal talcum powder products. In addition, the updated Sister Study analyses, with recall bias correction, showed a 40%, statistically significant, increased risk with lifetime assessment of genital talc use. Furthermore, risk of ovarian cancer was greater than 2 times higher in women with high frequency and/or high duration of use of genital talc, results that were statistically significant.

Viewed in the context of the high consistency of the study results across time, diverse study populations, and strong study designs, bias and chance as explanation for the increased risk are unlikely. Further, my confidence in the reliability of the data on magnitude of the risk is enhanced. Therefore, my analysis of these studies strongly supports a causal association and, given the high prevalence of use of talcum powder products in this population, these levels of risk present a clinically significant public health concern. I placed high weight on this aspect of determination of causality.

Consistency of the association: Across the case-control and cohort studies, the association between use of talcum powder products and risk of ovarian cancer was highly consistent. As indicated above, the case-control studies included population-based and hospital-based studies from a diverse geographic area across the U.S., as well as Australia, Canada, the UK, Israel, Greece, and China. Of the 28 studies, 24 found odds ratio greater than 1.1 for ovarian cancer in women who had any perineal exposure to talcum powder products, compared with never users (Cramer, Welch et al. 1982, Hartge, Hoover et al. 1983, Whittemore, Wu et al. 1988, Booth, Beral et al. 1989, Chen, Wu et al. 1992, Harlow, Cramer et al. 1992, Rosenblatt, Szklo et al. 1992, Cramer and Xu 1995, Purdie, Green et al. 1995, Shushan, Paltiel et al. 1996, Chang and Risch 1997, Cook, Kamb et al. 1997, Green, Purdie et al. 1997, Godard, Foulkes et al. 1998, Cramer, Liberman et al. 1999, Ness, Grisso et al. 2000, Mills, Riordan et al. 2004, Merritt, Green et al. 2008, Wu, Pearce et al. 2009, Rosenblatt, Weiss et al. 2011, Kurta, Moysich et al. 2012, Wu, Pearce et al. 2015, Cramer, Vitonis et al. 2016, Schildkraut, Abbott et al. 2016). Of these 24 odds ratio estimates, 16 were statistically significant (95% confidence intervals excluded 1.0 or p value $\leq$ 0.05). Among the 8 studies which were not statistically significant, 7 had a sample size lower than that estimated to be

needed to have power to detect a statistically significant result. Furthermore, the increased risk of ovarian cancer with use of talcum powder products has been seen in various race/ethnic groups as well as in diverse geographic areas around the world. The recent analysis of African-American and White women by Davis et al. showed that both African-American and White women have elevated risk of ovarian cancer if they had used talcum powder products in the genital area. (Davis, Bandera et al. 2021) While two of the cohort studies on average showed more attenuated relative risks of ovarian cancer in relation to use of talcum powder product use, these studies were not well designed to determine true risk for ovarian cancer and perineal talc use. Therefore, their results as a group do not negate the significant case-control study findings and the significant results of the meta-analyses and the pooled analyses. The Sister Study, with its updated lifetime exposure data and recall bias correction, found relative risks of ovarian cancer that were similar to or higher than those seen in many of the case-control studies. Therefore, on average, the cohort studies show considerable consistency with the case-control studies.

The comprehensive meta-analysis by Penninkilampi *et al.*, assessed consistency across the studies included in their analysis by measuring heterogeneity with Cochran's *Q* statistic, with $P < 0.10$ indicating heterogeneity. (Penninkilampi and Eslick 2018) They then quantified the degree of heterogeneity using the I^2 statistic. The I^2 statistic represents the fraction of the total variability across studies that is due to heterogeneity. The authors categorized I^2 values of 25%, 50%, and 75% as corresponding to low, moderate, and high degrees of heterogeneity, respectively, which is typical for meta-analyses. (Higgins and Thompson 2002) The authors found that there was no heterogeneity in the relative risk estimates for exposure to talcum powder products in the perineal area, or on diaphragms or sanitary napkins. Even though the 95% confidence intervals contained 1.0 in the cohort studies, given the clearly increased relative risk across the case-control studies, the trend toward increased risk in two of the three cohort studies, and the results from the Penninkilampi et al. meta-analysis, it is my opinion that this did not occur by chance but is, in fact, a true causal relationship.

The consistency across studies, led by many investigators, using different study designs, and in diverse ethnic, racial, and geographic populations over a period of nearly 35 years weighs heavily as to the consistency and reliability of the data in favor of a causal risk. Accordingly, I placed high weight on this factor in my causation analysis.

Specificity of the association: Use of talcum powder products is strongly associated with epithelial ovarian cancer. Analyses by histologic subtype of epithelial ovarian cancer found that serous ovarian cancer appeared to be most strongly and consistently related to talc exposure, although the pooled case-control project found associations some other subtypes of ovarian cancer. Mucinous cancers have been consistently found to be unrelated to use of these products. Therefore, the specificity aspect is present for epithelial ovarian cancer and certain subtypes. The Sister Study updated cohort analyses showed no increased risk of breast or uterine cancer, which supports specificity for ovarian cancer and genital talc exposure. However, because many carcinogens have been shown to cause diverse and nonspecific morbidities, such as smoking, I weighed this aspect moderately in my causal analysis as compared to other Bradford Hill factors.

Temporality: The epidemiologic studies that looked at lifetime talcum powder product use supported that exposure to these products predated the diagnosis of ovarian cancer. I did not find any evidence of 'reverse causation', e.g., using talcum powder products to alleviate symptoms associated with ovarian cancer, nor do any investigators report finding reverse causation. Importantly, symptoms related to ovarian cancer (bloating, increased abdominal size, abdominal pain, pelvic pain, difficulty eating, feeling full quickly) (Goff, Mandel et al. 2007) are not vaginal or perineal in origin, and would be unlikely to induce women to increase use of talcum powder products. The finding of temporality is an important component in the causal analysis and, as such, I place high weight in its applicability to the determination of causality.

Biologic gradient/ dose-response: The earlier studies were less likely to address dose-response associations. The larger, and more recent studies, however, collected important data that inform dose-response relationships. Many of the 28 case control studies found evidence of a dose-response effect. Most often, this took the form of lifetime numbers of applications of talcum powder products or years of use. Thus, while there were studies that did not look for or find a dose-response, the body of literature when taken as a whole does indicate a dose-response effect. Some studies did not gather detailed dose data such as frequency of use or length of use. Others gathered either frequency of the use or duration of use, but not both. As with smoking, ascertainment of frequency x duration of exposure (cumulative exposure) is an optimal metric to determine true dose-response effects. The meta-analyses and the pooled analysis also found evidence of relationships between increasing amount of exposure to talcum powder products in the perineal/genital area (including frequency, years of use,

and estimates of lifetime applications) and increased risk of developing epithelial ovarian cancer (i.e., dose-response relationships). The Sister Study cohort, with its lifetime genital talc exposure data, found strong, statistically significant increased risk of ovarian cancer with increasing frequency and with increasing duration of exposures, with p-trend tests that were statistically significant.

The most recent meta-analysis found that the highest frequency of exposure to talc in the perineal area was associated with the highest relative risk, which is indicative of dose-response.(Kadry Taher, Farhat et al. 2019) The authors, Taher et al, also estimated cumulative exposure with talc-years and stated that: "Overall, the graphical results …suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc…" The recent meta-analysis of Woolen et al found a statistically significant 47% increased risk of ovarian cancer in women who had frequent exposure to talc in the perineal area (2 or more times per week); (Woolen, Lazar et al. 2022) this strongly supports a dose-response effect since lower levels of exposure across studies show lower levels of elevated risk.

Thus, the studies that accurately determined use of talcum powder products revealed evidence of dose-response effects. When present, the finding of a biologic gradient/dose-response is helpful in determining causation. The findings within the study data, particularly meta-analyses and the pooled analysis, thus, supports my causal analysis and I placed high weight on this factor.

Plausibility: In my consideration of whether talcum powder products can cause cancer, I considered the data for biologically plausible mechanisms by which exposure to talc could result in ovarian cancer. In that regard, I assessed data and determined that talcum powder products can migrate from the perineum through the female genital tract to the ovaries; talcum powder products are found in ovarian and fallopian tube tissues; talcum powder products can induce an inflammatory response; and because of the inflammatory response, malignant transformation can occur. Support for these finding comes from reliable, peer-reviewed scientific literature which indicates that talcum powder products can migrate from the perineum up the genital tract to the fallopian tubes and ovaries and become imbedded in the ovarian tissue. Thus, it is biologically plausible that genital exposure to talcum powder products can result in exposure to the ovaries. The findings that ovarian cancer risk is highest in women with patent reproductive tracts supports the biological plausibility also.

Data also plausibly indicates that inhalation of talcum powder products can result in exposure leading to cancer, including mesothelioma. Studies also show that talcum powder products can be absorbed and transported via the lymphatic system or blood stream. Therefore, inhalation of talcum powder products could result in similar ovarian exposure. Published scientific data shows that talc reaches the ovary and becomes imbedded in the ovarian tissue. There are reliable data to support that talc induces an inflammatory response which mediates oxidative stress, release of cytokines and resulting genotoxicity which can induce malignant transformation. Further, the presence of asbestos and other constituents in the talcum powder products such as asbestos, heavy metals, and fragrance have been shown to induce cancer by similar mechanisms.

While I have considered the data that do not support the plausibility of talcum powder products' carcinogenicity, otherwise overwhelming and reliable evidence indicates that there are biologically plausible mechanisms by which talcum powder products can induce ovarian carcinogenicity. Talc and its constituents can reach the ovaries, induce an inflammatory response that leads to genotoxicity and to development of ovarian cancer. While this mechanism of carcinogenicity is not proven, it is highly biologically plausible based on the present scientific information and understanding. Therefore, I placed high weight on this aspect of determination of causality.

Coherence: The cause-and-effect interpretation of the data on talcum powder product use and risk of ovarian cancer clearly do not significantly conflict with the known facts about the natural history and biology of the disease. Increased inflammation has been linked to risk of ovarian cancer, and talc and other contents of talcum powder products elicit inflammatory responses within areas of the body in which they have been found (i.e. ovary, peritoneum, lymph nodes, etc.). These mechanisms are consistent with one another and the accepted understanding of the role of inflammation in carcinogenesis. While these factors support a causal association and my opinions in this regard, I do not weigh them quite as heavily as the strength and consistency of the association.

Experiment: As discussed above, the evidence from randomized controlled trials can provide strong support to observational evidence. However, here, randomized controlled trials are neither feasible nor ethical, similar to smoking and lung cancer. This is because ovarian cancer is a rare disease and typically takes decades to develop to be clinically diagnosable. In addition, because the effects of genital talcum powder product use could be harmful, it would be unethical to conduct a trial of this type. Furthermore,

the studies involving migration of talc, the inflammatory process and its association with carcinogenesis all contribute in a compelling manner to the causal analysis. While there are experimental data supporting causation from cell studies and animal models, given the inability to conduct experimental studies in humans to test effects of talcum powder products on ovarian cancer development, there are no human experimental data. Despite this, data from reliable observational studies as described in this report strongly support causation. Therefore, I placed slight weight to this aspect of determination of causality.

Analogy: As analogy to talc carcinogenesis, there is strong evidence of carcinogenic fibers, e.g. asbestos, causing ovarian cancer as determined by IARC and government agencies. (Nowak, Schmalfeldt et al. 2021) A mechanism proposed for talc carcinogenesis to the ovary, e.g., inflammation, is also a proposed mechanism for asbestos' carcinogenic effect on mesothelium to cause mesothelioma (IARC 2010 100C). (2010) I placed high weight on this aspect of causality determination.

CONCLUSION

In conclusion, it is my professional opinion, stated to a medical and scientific degree of certainty, that based on the totality of the evidence, which includes epidemiological, biological, pathological and mechanistic data, perineal use of talcum powder products can cause ovarian cancer.

Tables: Epidemiological Studies of Talcum Powder Product Use and Risk of Ovarian Cancer

Table 1: Case-Control Studies

Study	Country	No. Cases	No. Non-cases	Source of participants	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-response?
Schildkraut 2016 (Schildkraut, Abbott et al. 2016)	U.S.	584	745	Population	1.44 (1.11-1.86)	1.38 (1.03-1.85)	Yes, OR's: < 3600 apps 1.16 ≥ 3600 apps 1.67 p_{trend} < 0.01
Cramer 2016 (Cramer, Vitonis et al. 2016)	U.S.	2041	2100	Population	1.33 (1.16-1.52)	1.42 (a) (1.19-1.69)	Yes > 24 talc-years: OR 1.49 p_{trend} = 0.02
Wu 2015 (Wu, Pearce et al. 2015)	U.S.	1701	2391	Population	1.46 (1.27-1.69)	Not addressed	Yes, per 5-years talc: OR 1.14 (95% CI 1.09-1.20)
Kurta 2012 (Kurta, Moysich et al. 2012)	U.S.	902	1802	Population	1.4 (1.16–1.69)	Not addressed	Not addressed
Rosenblatt 2011 (Rosenblatt, Weiss et al. 2011)	U.S.	812	1313	Population	1.27 (0.97-1.66)	1.47 (borderline) (0.84-2.56) 1.01 (invasive) (0.69-1.47)	No (lifetime number of apps, years of use)
Wu 2009 (Wu, Pearce et al. 2009)	U.S.	609	688	Population	1.53 (1.13-2.09)	1.70 (1.27-2.28)	Yes, lifetime apps OR: <=5200: 1.20 >5200 to <=15600: 1.38 >15,600 to

							<=52000: 1.34 >52000: 1.99 p_{trend} = 0.0004
Moorman 2009 (Moorman, Palmieri et al. 2009)	U.S.	1114	1086	Population	Whites: 1.04 (0.82-1.33) Blacks: 1.19 (0.68-2.09)	Not addressed	Not addressed
Merritt 2008 (Merritt, Green et al. 2008)	Australia	1576	1509	Population	1.17 (1.01-1.36)	1.21 (1.03-1.44)	Yes, OR: None 1.0 > 0-10 yrs 1.13 > 10-25 yrs 1.08 > 25 yrs 1.29 p_{trend} = 0.02 (similar stat sign trend for serous)
Mills 2004 (Mills, Riordan et al. 2004)	U.S.	256	1122	Population	1.37 (1.02-1.85)	1.77 (1.12-2.8)	No (freq X dur), OR Never 1.0 Q1 1.03 Q2 1.81 Q3 1.74 Q4 1.06 p_{trend} = 0.05
Ness 2000 (Ness, Grisso et al. 2000)	U.S.	767	1367	Population	1.5 (1.1-2.0)	Not addressed	No (duration only)
Cramer 1999 (Cramer, Liberman et al. 1999)	U.S.	563	523	Population	1.60 (1.18 - 2.15)	1.38 (borderline) (0.82, 2.31) 1.70 (invasive) (1.22, 2.39)	Yes, lifetime apps when fallopian tubes patent: OR < 3000: 1.54 3000-10,000: 1.72 >10,000: 1.80
Wong	U.S.	499	755 (non-	Hospital	0.92 (.24-3.62)	1.2 (0.7-2.1)	No (duration only)

1999 (Wong, Hempling et al. 1999)			GYN cancer patients)				
Godard 1998 (Godard, Foulkes et al. 1998)	Canada	170	170	Population	2.49 (0.94-6.58)	Not addressed	Not addressed
Green 1997 (Green, Purdie et al. 1997)	Australia	824	855	Population	1.3 (1.1-1.6)	Not addressed	No (duration only, data not shown)
Cook 1997 (Cook, Kamb et al. 1997)	U.S.	313	422	Population	1.5 (1.1-2.3)	1.70 (1.1-2.50)	No (cumulative lifetime days)
Chang 1997 (Chang and Risch 1997)	Canada	450	564	Population	1.42 (1.08-1.86)	1.34 (0.96-1.85)	No (frequency or duration)
Shushan 1996 (Shushan, Paltiel et al. 1996)	Israel	200	408	Population	2.0 (p=0.04)	Not addressed	Not addressed
Cramer 1995 (Cramer and Xu 1995)	U.S.	450	454	Population	1.6 (1.2-2.1)	Not addressed	Not addressed
Purdie 1995 (Purdie, Green et al. 1995)	Australia	824	860	Population	1.27 (1.04-1.54)	Not addressed	Not addressed
Tzonou 1993 (Tzonou, Polychronopoulou et al. 1993)	Greece	189	200	Hospital	1.05 (0.28-3.98)	Not addressed	Not addressed
Rosenblatt 1992 (Rosenblatt, Szklo et al. 1992)	U.S.	77	46	Hospital	1.7 (0.7-3.9)	Not addressed	Yes: >= 37.4 years vs. < 37.4 years: OR 2.4
Chen	China	112	224	Population	3.9 (0.9-10.63)	Not addressed	Not addressed

1992 (Chen, Wu et al. 1992)							
Harlow 1992 (Harlow, Cramer et al. 1992)	U.S.	235	239	Population	1.5 (1.0-2.1)	1.4 (.9-2.2)	Yes, lifetime applications, OR: < 1000: 1.3 1000-10,000: 1.5 > 10,000: 1.8 p_{trend} = 0.09
Booth 1989 (Booth, Beral et al. 1989)	U.K.	235	451	Hospital	Daily 1.3 (0.8-1.0) Weekly 2.0 (1.3-3.4)	Not addressed	Yes, RR: Never 1.0 Rarely 0.9 Monthly 0.7 Weekly 2.0 Daily 1.3 p_{trend} = 0.05
Harlow 1989 (Harlow and Weiss 1989)	U.S.	116 border-line only	158	Population	1.1 (0.7-2.1)	Not addressed	Not addressed
Whittemore 1988 (Whittemore, Wu et al. 1988)	U.S.	188	539	Hospital + population	1.45 (p=0.06)	Not addressed	1-20 applications/ mo RR 1.27 (0.82-1.96) > 20 apps/mo RR 1.45 (0.94-2.22) No p_{trend} provided
Hartge 1983 (Hartge, Hoover et al. 1983)	U.S.	135	171	Hospital	2.5 (0.7-10.0)	Not addressed	Not addressed
Cramer 1982 (Cramer, Welch et al. 1982)	U.S.	215	215	Population	1.92 (1.27-2.89)	Not addressed	Not addressed

Table 2: Prospective Cohort Studies

Study Year Published	Country	No. Cases	No. Non-cases	Baseline Age	Years of Follow-up	RR All Ovarian Ca, Any Perineal Talc Use (95% CI)	RR Serous Invasive Ovarian Ca, Any Perineal Talc Use	Dose-response
Sister Study Gonzalez, 2016 (Gonzalez, O'Brien et al. 2016)	U.S.	154	41,500	54.8	Median 6.6 years	0.73 (0.44-1.21)	Not addressed	Not addressed
Sister Study Update (O'Brien, Wentzensen et al. 2024)	U.S.	292	40,536	Mean years of age: By genital talc use: No 55.6 Yes 55.8 Missing 53	Mean f/u years: By genital talc use: No: 12.9 Yes: 13.2 Missing: 9.4	Recall bias corrected: 1.4 (1.04-1.89	Recall bias corrected: 1.62 (1.06-2.48)	Yes, RRs Frequency use: Sometimes: 1.18 Frequent: 1.81 p-trend 0.001 Duration use: 1 decade: 1.17 2+ decades: 2.01 p-trend 0.001
Women's Health Initiative Houghton, 2014 (Houghton, Reeves et al. 2014)	U.S.	429	61,147	63.3	Mean 12.4 years	1.06 (0.87-1.28)	1.13 (0.84-1.51)	No (< 9 vs. 10+ years); no frequency data collected

Nurses Health Study Gertig, 2000 (Gertig, Hunter et al. 2000)	U.S.	307	78,323	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.09 (0.86-1.37) (ever use perineal talc vs. never use)	1.40 (1.02-1.91)	No (only frequency data collected, no duration data)
Nurses Health Study Gates, 2008 (Gates, Tworoger et al. 2008)	U.S.	210	600	36-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.24 (0.83-1.83) (≥1/wk vs. < 1/wk)	1.48 (0.82-2.68) (≥1/wk vs. < 1/wk)	Yes: RR's < 1/wk 0.98 1-6/wk 1.01 > 6/wk 1.44
Nurses Health Study Gates, 2010 (Gates, Rosner et al. 2010)	U.S.	797	78,323??	6-61 years in 1982 (year of talcum powder product use data collected)	Not provided	1.06 (0.89-1.28) (≥1/wk vs. < 1/wk)	1.06 (0.84-1.35)	Not addressed

Table 3: Meta-analyses

Study	Number of Studies	Number of Cases	Relative Risk All Ovarian Ca, Any Perineal Talc Use (95% CI)	Relative Risk Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response
Woolen (Woolen, Lazar et al. 2022)	11	6542	1.47 (1.31-1.65)	Not addressed	Yes (only frequent talc use vs. none was analyzed):
Taher 2019 (Kadry Taher, Farhat et al. 2019)	27	16,005	1.28 (1.20–1.37)	1.38 (1.22-1.56)	Yes, frequency: Low: 1.22 Medium: 1.22 High: 1.39
Penninkilampi 2018 (Penninkilampi and Eslick 2018)	27	14,311	1.31 (1.24-1.39)	1.32 (1.22-1.43)	Yes: OR 1.32 for < 3600 applications; OR 1.42 for > 3600 applications
Berge 2017 (Berge, Mundt et al. 2017)	27	Not provided, should be same as Penninkilami above	1.22 (1.13–1.30)	1.24 (1.15–1.34)	Yes for duration and frequency: 1) RR per 10-year use 1.16 (95% CI 1.07-1.26); 2) RR per weekly use 1.05 (95% CI 1.04-1.07)
Langseth 2008 (Langseth, Hankinson et al. 2008)	20	Not provided	1.35 (1.26-1.46)	Not addressed	Not addressed
Huncharek 2003 (Huncharek, Geschwind et al. 2003)	16	5260	1.33 (1.16-1.45)	Not addressed	No summary estimates calculated. Dose response addressed in 9/16 source studies: no dose-response apparent
Cramer 1999 (Cramer, Liberman et al. 1999)	14	3834	1.4 (1.2-1.5)	Not addressed	Not addressed

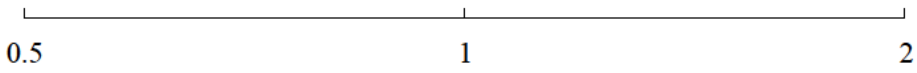
Gross 1995 (Gross and Berg 1995)	10 (N=5 studies with adjusted data and limited to epithelial ovarian cancers)	1509	1.29 (1.02-1.63)	Not addressed	Not addressed
Harlow 1992 (Harlow, Cramer et al. 1992)	6	1106	1.3 (1.1-1.6)	Not addressed	Not addressed

Table 4: Pooled Analyses

	Number of Studies	Number of Cases	Odds Ratio All Ovarian Ca, Any Perineal Talc Use (95% CI)	Odds Ratio Serous Ovarian Ca, Any Perineal Talc Use (95% CI)	Dose-Response All Ovarian Cancer
Davis 2021 (Davis, Bandera et al. 2021)	5	620 African-American; 2800 White	AA: 1.22 (0.97-1.53) Wh: 1.36 (1.19–1.57)	AA: 1.31 (1.01–1.71) Wh:1.33 (1.12–1.56)	No: similar associations for frequency (≤ 1/wk vs >1/wk) or duration (≤20 vs >20 yrs.)
Phung 2022 (Phung, Muthukumar et al. 2022)	9	8500	Without endometriosis: 1.12 (1.01-1.25) With endometriosis: 1.38 (1.04-1.84)	Not addressed	Not addressed
Terry 2013 (Terry, Karageorgi et al. 2013)	8	8,525	1.24 (1.15–1.33)	1.20 (invasive) (1.09–1.32)	Yes. OR (95% CI) by quartiles of lifetime applications vs. never use, non-mucinous cases only: Q1 1.18 (1.02-1.36) Q2 1.22 (1.06-1.41) Q3 1.22 (1.06-1.40) Q4 1.37 (1.19-1.58)
O'Brien 2020 (O'Brien, Tworoger et al. 2020)	4	2168	Overall: 1.08 (.99-1.17) Patent genital tract: 1.13 (1.01-1.26)	1.10 (0.97-1.25)	Unable to assess across all cohorts

Figure 1: Meta-Analyses and Pooled Analyses

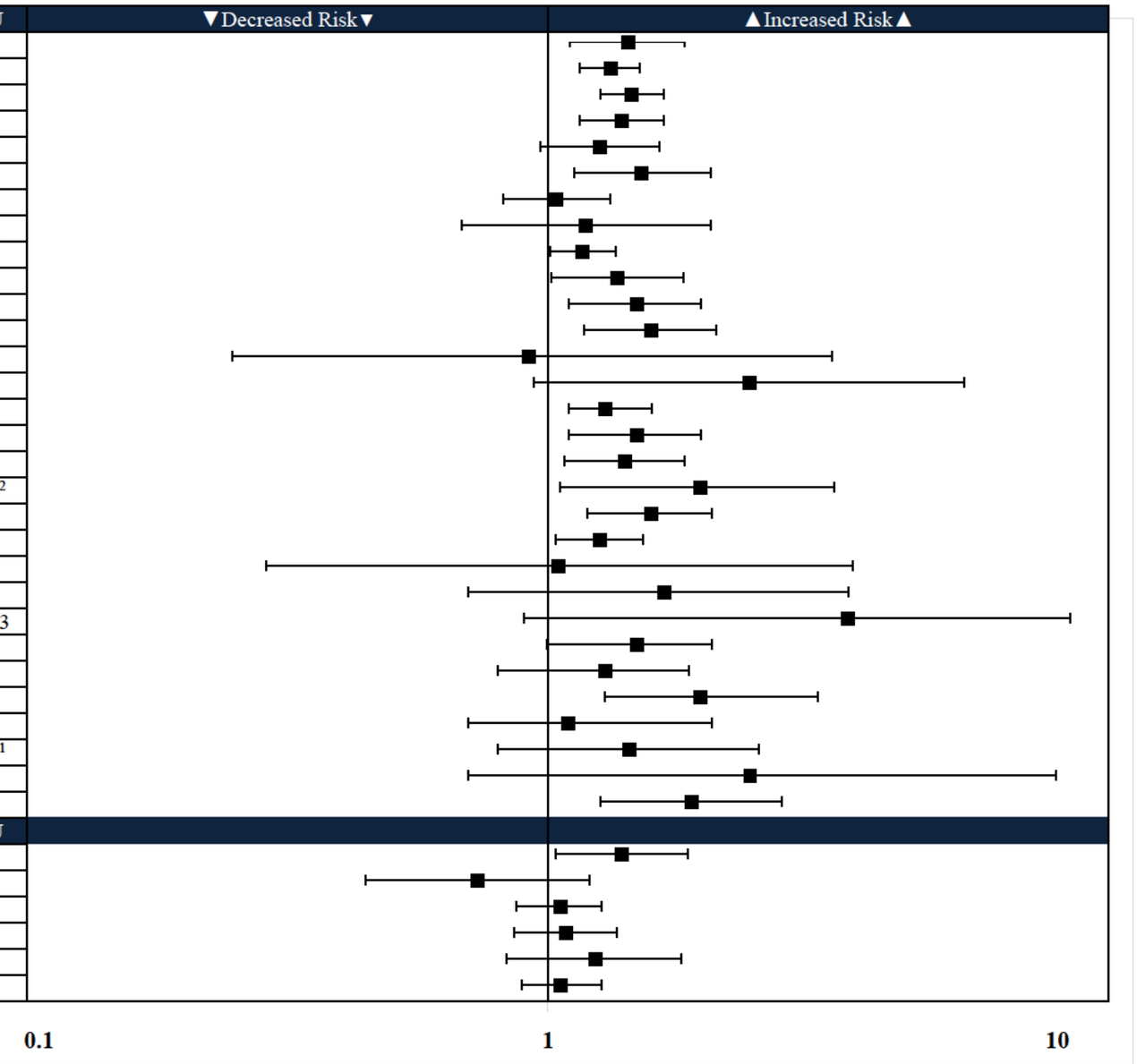
Meta-Analyses	Studies	Cases	DR	RR	CI L	CI U	▼Decreased Risk▼ ▲Increased Risk▲
Woolen (2022)	11	6,542	Yes	1.47	1.31	1.65	
Taher (2018)	27	17,149	Yes	1.28	1.2	1.37	
Penninkilampi (2018)	27	14,311	Yes	1.31	1.24	1.39	
Berge (2018)	27	N/A[1]	Yes	1.22	1.13	1.3	
Langseth (2008)	20	N/A[1]	N/A	1.35	1.26	1.46	
Huncharek (2003)	16	5,260	No[2]	1.33	1.16	1.45	
Cramer (1999)	14	3,834	N/A	1.4	1.2	1.5	
Gross (1995)	10[3]	1,509	N/A	1.29	1.02	1.63	
Harlow (1992)	6	1,106	N/A	1.3	1.1	1.6	
Pooled Analyses	**Studies**	**Cases**	**DR**	**RR**	**CI L**	**CI U**	
Terry (2013)	8	8,525	Yes	1.24	1.15	1.33	
O'Brien (2020)	4	2,168	No	1.08	0.99	1.17	
↳ Patent Reproductive Tract	4	1,384	Yes	1.13	1.01	1.26	
Davis (2021)	5	AA:620[4]	No	1.22	0.97	1.53	
		Wh:2,800[5]		1.36	1.19	1.57	



[1] Number of cases not provided.
[2] No summary estimates calculated. Dose response addressed in 9/16 source studies: no dose-response apparent.
[3] N=5 studies with adjusted data and limited to epithelial ovarian cancers.
[4] African American
[5] White

Figure 2: Case-Control and Cohort Studies

Case-Control Studies	Natl	Cases	Controls	Pop	DR	RR	CI L	CI U
Schildkraut (2016)	US	584	745	Pop.	Yes	1.44	1.11	1.86
Cramer (2016)	US	2041	2100	Pop.	Yes	1.33	1.16	1.52
Wu (2015)	US	1791	2391	Pop.	Yes	1.46	1.27	1.69
Kurta (2012)	US	902	1802	Pop.	N/A	1.4	1.16	1.69
Rosenblatt (2011)	US	812	1313	Pop.	No	1.27	0.97	1.66
Wu (2009)	US	609	688	Pop.	Yes	1.53	1.13	2.09
Moorman (2009) - Wh	US	1114	1086	Pop.	N/A	1.04	0.82	1.33
Moorman (2009) - AA	US	1114	1086	Pop.	N/A	1.19	0.68	2.09
Merritt (2008)	Aus	1576	1509	Pop.	Yes	1.17	1.01	1.36
Mills (2004)	US	256	1122	Pop.	No	1.37	1.02	1.85
Ness (2000)	US	767	1367	Pop.	Incpl	1.5	1.1	2.0
Cramer (1999)	US	563	523	Pop.	Yes	1.6	1.18	2.15
Wong (1999)	US	499	755	Hosp.	Incpl	0.92	0.24	3.62
Godard (1998)	Can	170	170	Pop.	N/A	2.49	0.94	6.58
Green (1997)	Aus	824	855	Pop.	Incpl	1.3	1.1	1.6
Cook (1997)	US	313	422	Pop.	No	1.5	1.1	2.0[6]
Chang (1997)	Can	450	564	Pop.	No	1.42	1.08	1.86
Shushan (1996)	Isr	200	408	Pop.	N/A	2	1.06[7]	3.66[2]
Cramer (1995)	US	450	454	Pop.	N/A	1.6	1.2	2.1
Purdie (1995)	Aus	824	860	Pop.	N/A	1.27	1.04	1.54
Tzonou (1993)	Gre	189	200	Hosp.	N/A	1.05	0.28	3.98
Rosenblatt (1992)	US	77	46	Hosp.	Yes	1.7	0.7	3.9
Chen (1992)	Chn	112	224	Pop.	N/A	3.9	0.9	10.63
Harlow (1992)	US	235	239	Pop.	Yes	1.5	1.0	2.1
Booth (1989) – daily	UK	235	451	Hosp.	Yes	1.3	0.8	1.9[1]
Booth (1989) – wkly	UK	235	451	Hosp.	Yes	2.0	1.3	3.4
Harlow (1989)	US	116	158	Pop.	N/A	1.1	0.7	2.1
Whittemore (1988)	US	188	539	H&P	Yes	1.45	0.81[1]	2.60[1]
Hartge (1983)	US	135	171	Hosp.	N/A	2.5	0.7	10.0
Cramer (1982)	US	215	215	Pop.	N/A	1.92	1.27	2.89
Cohort Studies	**Natl**	**Cases**	**Non**	**Flw Up**	**DR**	**RR**	**CI L**	**CI U**
O'Brien (2024)	US	292	40,536	13	Yes	1.4	1.04	1.89
Gonzalez (2016)	US	154	41,500	6.6	N/A	0.73	0.44	1.2[1]
Houghton (2014)	US	429	61,147	12.4	Incpl	1.06	0.87	1.28
Gertig (2000)	US	307	78,323	N/A	Incpl	1.09	0.86	1.37
Gates (2008)	US	210	600	N/A	Yes	1.24	0.83	1.83
Gates (2010)	US	797	78,323?	N/A	N/A	1.06	0.89	1.28



[6] Corrected data-point from study text (report figure: Cook 1997 CI Upper 2.3; Gonzalez CI Upper 1.21; Booth 1989 CI Upper 1.0; Whittemore CI p=0.06).
[7] Corrected data-point from defense expert report(s) (report figure: p=0.04).

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Additional Materials and Data Considered

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2. American Cancer Society - Ovarian Cancer
3. Begg, March. Cause and association: missing the forest for the trees
4. Boorman G, J Seely. The lack of an ovarian effect of lifetime talc exposure in F344/N Rats and B6C3F1 Mice
5. Carr CJ. Talc: consumer uses and health perspectives
6. Chang, et al. Occupational exposure to talc increases the risk of lung cancer: a meta-analysis of occupational cohort studies
7. CIR Final Report - Safety assessment of talc as used in cosmetics
8. Cralley, Key et al. Fibrous and mineral content of cosmetic talcum products
9. Current Intelligence Bulletin 62 - Asbestos fibers and other elongate mineral particles: state of the science and roadmap for research
10. Deposition Transcript - Shripal Sharma (Berg v. J&J)
11. Deposition Transcript & Exhibits - John Hopkins (8/16/18, 8/17/18, 10/26/18, 11/5/18)
12. Deposition Transcript & Exhibits - Joshua Muscat (9/25/18)
13. Deposition Transcript & Exhibits - Julie Pier (9/12/18, 9/13/18)
14. Deposition Transcript & Exhibits - Linda Loretz (7/17/18, 10/1/18, 10/2/18)
15. Deposition Transcript of Alice Blount, April 2018
16. Deposition Transcript of Patricia Moorman (Ingham)
17. Expert Report of Jack Siemiatycki
18. Fair warning TalcDoc 15
19. Fair warning TalcDoc 5 - Exhibit 113 (JNJNL91_000022019)
20. Fiber exposure during use of baby powders - Dement, Shuler, Zumwalde - NIOSH

21. First Amended Master Long Form Complaint & Exhibits
22. Fiume et al. Safety assessment of talc as used in cosmetics
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30. Harper A, G Saed. Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes - Abstract, Society of Gynecologic Oncology, 2018, in press.
31. Hartge et al. Talc and ovarian cancer
32. Heller et al. The relationship between perineal cosmetic talc usage and ovarian talc particle burden
33. Henderson et al. Talc and Carcinoma of the Ovary and Cervix
34. Henderson et al. Talc in normal and malignant ovarian tissue
35. Hernan. The C-Word: scientific euphemisms do not improve causal inference from observational data
36. Hopkins Chart - Exhibit 24
37. Huncharek et al. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies
38. IARC - Monograph Vol. 93 - Carbon black, titanium dioxide, and talc, 2010
39. IOM (National Academies of Sciences, Engineering and Medicine). Ovarian Cancers: Evolving paradigms in research and care
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50. JNJ000526231-JNJ000526676
51. JNJ000637879-JNJ000637881
52. JNJAZ55_000000577-JNJAZ55_000000596
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56. JNJI4T5_000004099-JNJI4T5_000004100
57. JNJMX68_000004996-JNJMX68_000005044
58. JNJMX68_000004996-JNJMX68_000005044
59. JNJNL61_000001534-JNJNL61_000001535
60. JNJNL61_000006431-JNJNL61_000006432
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70. Letter from Personal Care Products Council to FDA re: Comments on citizen's petition to the Commissioner of the Food and Drug Administration seeking a cancer warning on Talc products
71. "Levin. ""Baby powder battles: Johnson & Johnson internal documents reveal asbestos worries""
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73. Lockey. Nonasbestos fibrous minerals
74. Longo, Young. Cosmetic talc and ovarian cancer
75. Loretz Exhibit 105
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77. Loretz Exhibit 107
78. Loretz Exhibit 108
79. Lundin, Dossus, Clendenen et al. C-reactive protein and ovarian cancer: a prospective study nested in three cohorts (Sweden, USA, Italy)
80. Mallen, Townsend, Tworoger. Risk factors for ovarian carcinoma
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88. Narod, Steven A. 2016. "Talc and Ovarian Cancer." Gynecologic Oncology 141(3):410-12. https://doi.org/10.1016/j.ygyno.2016.04.011.
89. Ness, Cottreau. Possible role of ovarian epithelial inflammation in ovarian cancer
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103. Trabert, Britton, Elizabeth M. Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L. Anderson, Theodore M. Brasky, et al. 2019."Analgesic use and ovarian cancer risk: an analysis in the ovarian cancer cohort consortium." Journal of the National Cancer Institute 111(2). Https//doi.org/10.1093/jnci/djy100
104. Trial Testimony of John Hopkins, Berg v. J&J (Oct. 2013)
105. US Dept. of Health & Human Service - Public Health Service, Agency for Toxic Substances and Disease Registry - "Toxicological profile for asbestos"
106. Van Gosen, Lowers et al. Using the geologic setting of talc deposits as an indicator of amphibole asbestos content
107. Virta. The phase relationship of talc and amphiboles in a fibrous talc sample
108. WCD000254-WCD000255
109. Wehner, Hall et al. Do particles translocate from the vagina to the oviducts and beyond?
110. Werner. Presence of asbestos in talc samples
111. Whysner, J., and M. Mohan. 2000. "Perineal application of talc and cornstarch powders: evaluation of ovarian cancer risk." American Journal of Obstetrics and Gynecology 182 (3):720-24
112. Wu, Song, Wei Zhu, Patricia Thompson, and Yusuf A. Hannun. 2018. "Evaluating intrinsic and non-intrinsic cancer risk factors." Nature Communications 9(1):3490. Https://doi.org/10.1038/s41467-078-05467-z
113. Zuckerman D, D Shapiro. Talcum powder and ovarian cancer, National Center for Health Research, May 7, 2018. http//www.center4research.org/talcum-powder-ovarian-cancer/

EXHIBIT A

Curriculum Vitae

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EDUCATIONAL BACKGROUND

Residency, Primary Care Internal Medicine, 6/92, University of Washington School of Medicine, Seattle, WA
M.D., 6/89, New York Medical College, Valhalla, NY
Ph.D. in Epidemiology, 12/82, University of Washington, Seattle, WA
M.A. in Medical Sociology, 6/76, State University of New York at Buffalo,
B.A. in Sociology, 1/74, Boston University, Boston, MA

PROFESSIONAL POSITIONS

Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA
- Director, FHCRC Prevention Center (2002 - 2012)
- Full Professor (2001 - present)
- Associate Member (1997 – 2001)
- Assistant Member (1996 - 1997)
- Senior Staff Scientist, Associate in (1983 – 1985; 1992 - 1996)

Department of Epidemiology, University of Washington School of Public Health, Seattle, WA
- Research Professor (2003 -)
- Research Associate Professor (1999 – 2003)
- Research Assistant Professor (1996 - 1999)
- Clinical Instructor (1992 - 1996)

Department of Medicine, Division of Geriatrics
- Adjunct Research Professor (2003 -)
- Adjunct Research Associate Professor (1999 - 2003)

Department of Medicine, Division of General Internal Medicine
- Clinical Instructor (1992 – 1996)

Clinical Nutrition Research Unit, University of Washington, Seattle WA
- Affiliate Investigator (1996 – present)

Harborview Medical Center, Adult Medicine Clinic, Seattle, WA
- Attending Physician (1992 - 1995)

University of Washington, Women's Primary Care Clinic, Seattle, WA
- Attending Physician (1996)

HONORS and TRAINEESHIPS

- American College of Sports Medicine Citation Award, 2012
- McDougall Mentoring Award, Fred Hutchinson Cancer Research Center, 2011
- Komen for the Cure Scientific Advisory Council/Komen Scholars, 2010-2012
- University of Washington Roger E. Moe Award for Translational Research 2009
- The Joan P. Liman MD Award, Recipient, New York Medical College, 1989
- National Institute for Dental Research, Fellowship Award in Behavioral Dental Research, 1983
- National Cancer Institute Traineeship, 1980-1982
- University of Washington Public Health Traineeship, 1978-1979

PROFESSIONAL ACTIVITIES

Committee Memberships and Academic Consulting

- 2018 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2016-2018
- Member, External Advisory Board, Pennington Biomedical Research Center, Louisiana, 2018
- Reviewer, NIEHS Sisters Study, 2018
- Patient-Centered Outcomes Research Institute Advisory Panel on Clinical Trials, 2014-2016
- University of Alabama, Center for Exercise Medicine External Advisory Committee, 2016
- Program Committee Member, American Institute for Cancer Research 2016 Conference on Nutrition, Physical Activity, Obesity and Cancer
- Consortium Member: NCI Randomized Controlled Trials of Lifestyle Weight Loss Interventions for Genome-Wide Association Studies, 2016-
- AACR Cancer Prevention Committee, 2010-2015
- World Cancer Research Fund (WCRF) Continuous Update Project Panel, 2010-2021
- 2008 U.S. Dept. Health and Human Services Physical Activity Guidelines Advisory Committee, 2007- 2008 (Chair, Cancer Working Group)
- Cancer Prevention Research Institute of Texas, Prevention Review Committee, 2009-2015
- Chair, Transdisciplinary Research on Energetics and Cancer (TREC) Steering Committee 2006-7
- Chair, Cancer Interest group, the Obesity Society, 2006-7
- Steering Committee for International Position Paper and Consensus Conference on Women's Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998 – 2002
- International Advisory Board to the 4th International Symposium on Women's Health and Menopause, 2000 – 2001 and 2004
- Professional Advisory Committee, Breastcancer.org, 2003 –2017
- Women's Health Research Coalition, 2002
- Women's Health Initiative Committee Membership: Morbidity and Mortality (Co-Chair); Performance Monitoring Outcomes Committee (Chair); Coordinating Center Outcomes Scientific Committee (Chair); Coordinating Center Representative to WHI Program Advisory Committee, 1994-1995; Genetics Working Group; Cancer Biomarkers Working Group
- Consultant, *Moving Forward Study*, University of Illinois, Chicago (PI, Melinda Stolley), 2013-
- Consultant, *The Energy Balance and Breast Cancer Aspects studies: EBBA-I and EBBA-II*, Oslo University Hospital, Oslo, Norway (PI, Inger Thune), 2013-
- American Institute of Cancer Research Meeting Program Committee member, 2010, 2016
- Cancer Prevention Expert Panel, Pennington Biomedical Research Center (Baton Rouge, LA), 2010
- External Advisory Committee, Cooper Clinic, Dallas, Tx, April 2006
- Steering Committee, LISA Trial of Weight Loss for Breast Cancer Patients, Novartis Canada 2005 – 2007
- Chair, Breast Clinical Endpoints Committee, DANCE trial of testosterone patch safety, Proctor & Gamble, 2006-7
- External Reviewer for NCI Nutritional Epidemiology Program, 2005, 2013
- Data and Safety Monitoring Board, "Project Alive", Kaiser Oakland (B. Sternfeld, PI)
- Member, NCI Transdisciplinary Research Working Group, co-Chair section on Lifestyle, 2006
- Panels for American Cancer Society Guidelines on *Diet, Nutrition and Cancer Prevention* and Guidelines for Cancer Patients and Survivors (2001, 2003, 2005)
- Working Group for International Agency for Research on Cancer Handbook of Cancer Prevention: Volume 6 – Weight control and physical activity, 2000 – 2001
- Advisory Board for the Tomorrow Study (Alberta, Canada, Cancer Cohort Study), 1999 - 2001
- Advisor to The effects of weight loss and exercise on biomarkers of breast cancer risk- a randomized pilot trial (M. Harvie, A. Howell, Manchester, England)
- Participant, "Workshop on Physical Activity and Breast Cancer", National Action Plan on Breast Cancer, Nov. 1997
- Invitee, "Beyond Hunt Valley: Research on Women's Health for the 21st Century", Nov. 1997
- Participant, "Breast Cancer in Minorities", National Action Plan on Breast Cancer, March 1999

- 2005 ASPO Annual Meeting Program Committee
- Member, Steering Committee for International Position Paper and Consensus Conference on Women's Health and the Menopause, NHLBI-Lorenzi Foundation sponsors, 1998

Editorial Boards

- AACR, Cancer Prevention Research, 2008 - 2014
- Journal of Women's Health, 1998 –
- Medscape Women's Health and Ob/Gyn & Women's Health, 2001 – 2002

Grant Reviewing

- Co-Chair, Breast Cancer Research Foundation Precision Prevention Initiative, 2023
- Chair, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2017
- Member, Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Prevention, January 2018
- Florida Department of Health Research Program Peer Review, 2017
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program - Epidemiology, February, 2016
- NCI Omnibus: Biomarkers R03 & R21 SEP-12 Review Committee 2015
- NCI Omnibus: Cancer Management & Behavior 2014
- MD Anderson NCI CCSG Review 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Breakthrough Award, Epidemiology/Prevention 2013
- Department of Defense (DOD) United States Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) Breast Cancer Research Program Training-Epidemiology - Prevention (2 cycles) 2013
- NIH Special Emphasis Panel Member September 2012
- NIH PRDP Study Section Member 2008-2012 (ad hoc 2006-2008)
- Susan G. Komen for the Cure 2009 - 2013
- Cancer Prevention & Research Institute of Texas 2009 – 2015
- Qatar National Priorities Research Program 2010-2013
- Catalan TV3 Marató Call 2005, 2013
- San Diego State/UC San Diego Pilot Grant Reviewer 2012
- FHCRC and UW Pilot Grant Reviews yearly
- NCI Cancer Centers Review Group Ad Hoc Member May 2007
- Pennsylvania Interim Performance Review 2007, 2008, 2010, 2012
- Marsha Rivkin Center for Ovarian Cancer Research Grants 2012
- Memorial Sloan Kettering Cancer Center NCI CCSG Review 2007
- Department of Defense Breast Cancer Program Predoctoral Fellowship Grants, 2006
- Chair, NIH Special Study Section "Mechanisms of Physical Activity Behavior Change" 3/04
- NIH EDC-2 Special Study Section, Sept. 9-10, 1997
- Alberta Cancer Board Grants, 1998-2002 and other Canadian agencies, and for Spanish and Italian Foundations
- NCI Administrative Supplements for Disseminating Evidence-based Research Products 8/04
- Member, ACSM Research Review Committee 2004 – 2006

Journal Reviewing

- JAMA, Journal of Clinical Oncology, Obesity, Archives of Internal Medicine, American Journal of Epidemiology, Journal of the National Cancer Institute, Annals of Internal Medicine, European Journal of Cancer,

British Journal of Cancer, Cancer Causes & Control, Cancer Epidemiology Biomarkers & Prevention, Annals of Epidemiology, Epidemiology, Nutrition, American Journal of Clinical Nutrition, Cancer Prevention Research, Nature, Breast Cancer Research, Journal of Women's Health, Clinical Cancer Research

College Fellowship and Membership

- The Obesity Society (Fellow 2003 -)
- American College of Sports Medicine (Fellow 2003 -)
- American College of Epidemiology (Fellow 1999 -)

Professional Licenses and Certification

- Board Certified, American Board of Internal Medicine, 1992
- Physician & Surgeon License, State of Washington, 7/21/91-2/18/21
- DEA License, Expires 2023, Schedules 2, 2N, 3, 3N, 4, 5

LEADERSHIP

- Director, FHCRC Prevention Center, 2002-2012
- Chair, TREC Steering Committee 2006-7
- Chair, Cancer Interest Group, Obesity Society 2007-8
- Chair, Cancer Subcommittee, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Member, Leadership Group, DHHS Physical Activity Guidelines Advisory Committee 2016-18
- Chair, Cancer Working Group, DHHS Physical Activity Guidelines Advisory Committee 2007-8
- Chair, Section on Mechanisms, IARC Handbook of Cancer Prevention 2002: Physical Activity and Weight Control, 2000-1
- Organized and Chaired Symposium on Physical Activity and Cancer, American College of Sports Medicine, St. Louis, June 2002

REFEREED PUBLICATIONS

(** refers to student papers under my supervision; ^ denotes papers from studies on which I was PI)

1983

1. Shy K, **McTiernan A**, Daling J, and Weiss N: Oral contraceptive use and the occurrence of pituitary prolactinoma. Journal of the American Medical Association 249:2204-2207, 1983.

1984

2. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to reproductive and hormonal factors. American Journal of Epidemiology 120:423-435, 1984.
3. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid carcinoma in women in relation to radiation exposure and history of thyroid disease. Journal of the National Cancer Institute 73:575-581, 1984.

1985

4. **McTiernan A**, Chu J, and Thomas D: Cancer in whites in the Pacific Basin. In Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin. National Cancer Institute Monograph 69:65-72, 1985.

1986

5. ^**McTiernan A**, Weiss N, and Daling J: Bias resulting from using the card-back system to contact patients in epidemiologic studies. American Journal of Public Health 76:71-73, 1986.
6. **McTiernan A**, Whitehead A, Thomas D, and Noonan E: Efficient selection of controls for multi-centered collaborative studies of rare diseases. American Journal of Epidemiology 123:901-904, 1986.
7. **McTiernan A**, Thomas D, Johnson L, and Roseman D: Risk factors for estrogen receptor-rich and estrogen receptor-poor breast cancers. Journal of the National Cancer Institute 77:849-854, 1986.
8. **McTiernan A** and Thomas D: Evidence for a protective effect of long-term lactation on risk of breast cancer: results from a case-control study. American Journal of Epidemiology 124:353-358, 1986.
9. ^Mueller B, **McTiernan A**, and Daling J: Level of response in epidemiologic studies using the card-back system to contact patients. American Journal of Public Health 76:1331-1332, 1986.
10. Vaughan T, and **McTiernan A**: Diet in the etiology of cancer. Sem. Oncol. Nursing 2:3-13, 1986.

1987

11. ^**McTiernan A**, Weiss N, and Daling J: Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. Cancer Research 47:292-295, 1987.

1991

12. Rosenblatt KA, Thomas DB, **McTiernan A**, et al: Breast cancer in men: aspects of familial aggregation. Journal of the National Cancer Institute 83:849-54, 1991.
13. Demers PA, Thomas DB, Rosenblatt KA, **McTiernan A**, et al: Occupational exposure to electromagnetic fields and breast cancer in men. American Journal of Epidemiology 134:340-47, 1991.

1992

14. Thomas DB, Jiminez LM, **McTiernan A**, et al: Breast cancer in men: risk factors with hormonal implications. American Journal of Epidemiology 135:734-48, 1992.

1993

15. Stalsberg H, Thomas DB, Rosenblatt KA, Jiminez LM, **McTiernan A**, et al: Histologic types and hormone receptors in breast cancer in men--a population-based study in 282 North American men. Cancer Causes and Control 4:143-51, 1993.

1994

16. Thomas DB, Rosenblatt K, Jiminez LM, **McTiernan A**, et al: Ionizing radiation and breast cancer in men. Cancer Causes and Control 5:9-14, 1994.

1995

17. Bowen D, Green P, Kestin M, **McTiernan A**, Carroll D: Effects of decreasing dietary fat on psychological well-being. Cancer Epidemiology, Biomarkers, and Prevention 4:555-59, 1995.
18. **McTiernan A**, Rossouw J, Manson J, et al: Informed consent in the Women's Health Initiative. Journal of Women's Health 5:519-529, 1995.

1996

19. Prentice R, Rossouw JR, Johnson, SR, Freedman LS, **McTiernan A**. The role of randomized controlled trial in assessing the benefits and risks of long-term hormone replacement therapy: example of the Women's Health Initiative. Menopause, 1996;3:71-76.
20. **McTiernan A**, Stanford JL, Weiss NS, Daling JR, Voigt LF: Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. Epidemiology 1996;7:598-604.

1997

21. Burke W, Peterson G, Lynch P, Botkin J, Daly M, Garber J, Kahn MJE, **McTiernan A**, Offitt K, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 1. Hereditary nonpolyposis colon cancer. JAMA 1997;277:915-919.
22. Burke W, Daly M, Garber J, Botkin J, Kahn MJE, Lynch P, **McTiernan A**, Offitt K, Perlman J, Petersen G, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. 2. BRCA1 and BRCA2. JAMA 1997;277:997-1003.
23. **McTiernan A**, Gilligan M, Redmond C: Assessing individual risk for breast cancer: risky business. J Clinical Epidemiology 1997;50:547-556.
24. **McTiernan, A**. Physical activity and breast cancer – time to get moving? (editorial) NEJM 336:1311-1312, 1997.
25. **McTiernan, A**. Commentary on: Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. Clin J Sport Med 1997;7 (4) 315

1998

26. Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clinical Trials 1998;19:61-109.
27. **McTiernan A**, Stanford J, Daling J, Voigt L: Prevalence and correlates of physical activity in women aged 50-64 years. Menopause 1998;5:95-101.
28. ^**McTiernan A**, Kumai C, Bean D, Hastings R, Schwartz R, Ulrich N, Gralow J, Potter J. Anthropometric and hormone effects of an 8-week exercise-diet intervention in breast cancer patients: results of a feasibility pilot study. Cancer Epidemiology Biomarkers Prevention 1998;7:477-81.
29. Hoffman-Goetz L, Apter D, Demark-Wahnefried W, Goran M, **McTiernan A**, Reichman M. Mechanisms for an association between physical activity and breast cancer. Cancer (supplement) 1998;83:621-628.
30. **McTiernan A**, Ulrich N, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes and Control 1998;9(5)487-509.

1999

31. Cheblowski RT, **McTiernan A.** Elements of informed consent for Hormone Replacement Therapy in patients with diagnosed breast cancer. Journal of Clinical Oncology 1999;17(1):130-42.
32. ^Negri E, Ron E, Franceschi S, DalMaso L, Mark SD, Preston-Martin S, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies: Methods. Cancer Causes and Controls 1999:10:131-142.
33. ^Negri E, DalMaso L, Ron E, LaVecchia C, Mark SD, Preston-Martin S, **McTiernan A**, et al. Menstrual and reproductive factors and thyroid cancer. Cancer Causes and Controls 1999:10:143-155.
34. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. Oral contraceptives, menopausal replacement treatment and other female hormones and thyroid cancer. Cancer Causes and Controls 1999:10:157-166.
35. Durfy S, Bowen D, Burke W, **McTiernan A,** et al. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in Western Washington. Cancer Epidemiology Biomarkers and Prevention 1999:8;369-376.
36. ^**McTiernan A**, Ulrich CM, Yancey D, Slate S, Nakamura H, Oestreicher N, Bowen D, Yasui Y, Potter J, and Schwartz R. The Physical Activity for Total Health (PATH) Study: rationale and design. Medicine and Science in Sports and Exercise 1999;31:1307-1312.
37. **McTiernan A**, Potter J, Bowen D, Schwartz R. Exercise clinical trials in cancer prevention research: a call to action. Cancer Epidemiology Biomarkers and Prevention 1999; 8:201-207.
38. Bowen D, **McTiernan A**, Burke W, Powers D, Pruski J, Durfy S, Gralow J, Malone K. Participation in breast cancer risk counseling among women with a family history. Cancer Epidemiology Biomarkers and Prevention 1999; 8:581-586.
39. Rosenblatt KA, Thomas DB, Jimeneq LM, Fish B, **McTiernan A**, et al. Diet and breast cancer in men. Cancer Causes and Control 1999;10:107-113.
40. ^Franceschi S, Preston-Martin S, DalMaso L, Negri E, LaVecchia C, **McTiernan A**, et al. A pooled analysis of thyroid cancer case-control studies. IV. Benign thyroid diseases. Cancer Causes and Control 1999;10:583-595.
41. ^LaVecchia C, Ron E, Franceschi S, DalMaso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, **McTiernan A**. A pooled analysis of thyroid cancer studies. Anthropometric factors. Cancer Causes and Control 1999;10:583-595.

2000

42. Burke W, Culver JB, Bowen D, Lowry D, Durfy S, **McTiernan A**, Anderson, MR. Genetic counseling for women with an intermediate family history of breast cancer. American Journal of Medical Genetics 2000;90(5):361-8.
43. **McTiernan A.** The associations of energy balance and body mass index with breast cancer risk in United States women from diverse racial and ethnic backgrounds. Cancer 2000;88:1248-1255.
44. Bowen DJ, **McTiernan A**, , Rosenberg E, Powers P, Feng Z: Recruiting women into a smoking cessation program to control weight: who might quit? Women and Health 2000;31(4):41-58.
45. Wingo PA, Calle EE, **McTiernan A**. How does breast cancer mortality compare with other cancers and cardiovascular disease at different ages in U.S. women? Journal of Women's Health 2000;9:999-1006.
46. **McTiernan A.** Physical Activity and the Prevention of Breast Cancer. Medscape. Invited as Expert Opinion. October 2000; 5(5). Available at http://www.medscape.com/Medscape/WomensHealth/journal/2000/v05.n05/wh7419.mcti/wh7419.mcti-01.html

2001

47. **Young SYN, Gunzenhauser JD, Malone KE, **McTiernan A.** The relationship between body mass index and asthma in the military population of the northwestern United States. Archives Internal Medicine 2001;161:1605-1611.
48. Davidoff R, **McTiernan A**, Constantine G, Davis KD, Balady GJ, Mendes LA, Rudolph RE, Bowen, DJ. Echocardiographic evaluation of women previously treated with fenfluramine: Long-term follow-up of a randomized, double-blind, placebo-controlled trial. Archives of Internal Medicine. 2001;161:1429-1436.
49. Marrett L, Theis B, Ashbury FD, and an Expert Panel. Workshop report: physical activity and cancer prevention. (member of the expert panel). Chronic Diseases in Canada 2001;21:143-149.
50. La Vecchia C, Brinton L, **McTiernan A**. Menopause, hormone replacement therapy and cancer. Maturitas 2001; 39: 97-115.
51. **McTiernan A,** Burke W, Bars J, et al. Comparison of two breast cancer risk estimates in women with a family history of breast cancer. Cancer Epidemiology Biomarkers and Prevention 2001;10: 333-338.
52. ^Bosetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, **McTiernan A**, Land C, Mabuchi K, Jin F, Wingren G, Hallquist H, Glattre E, Lund E, Levi F, Linos D, La Vecchia

C. A pooled analysis of case-control studies of thyroid cancer: fish and shellfish consumption. Cancer Causes and Control 2001;12:375-382.

53. Shors AR, Solomon C, **McTiernan A**, White E. Melanoma risk in relation to height, weight, and exercise (United States) Cancer Causes and Control 2001; 12(7):599-606. Cancer Causes Control. 2001 Sep;12(7):599-606.
54. Tavani A, La Vecchia C, Brinton LA, **McTiernan A.** Hormone replacement therapy and risk of endometrial cancer. Tumori. 2001 Sep-Oct;87(5):S20-1.
55. LaVecchia C, Brinton LA, **McTiernan A**. Hormone replacement therapy and breast cancer risk: epidemiology. Journal fur Menopause 2001;8:5-7.
56. Friedenreich C, Marrett LD, Members of the Canadian Breast Cancer Initiative Working Group on Primary Prevention of Breast Cancer and an Expert Panel. Workshop report: identification of research needs in breast cancer etiology. Chronic Diseases in Canada 2001;22:41-49 (member of the Expert Panel).

2002

57. ^**Irwin ML, **McTiernan A**. Exercise effect on body weight in postmenopausal women: the Physical Activity for Total Health Study. In RA Lobo, PG Crosignani, R Paoletti, F Bruschi (eds). Women's Health and Menopause: New Strategies – Improved Quality of Life, Dordrecht, Kluwer Academic Pub. 2002, pp. 345-352.
58. Chlebowski RT, Aiello E, **McTiernan A.** Weight loss in breast cancer patient management. J. Clinical Oncology 2002;20(4):1128-1143.
59. ^**Slate S, Yasui Y, Ulrich C, **McTiernan A**. Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers. Cancer Epidemiology Biomarkers and Prevention 2002; 11: 73-77.
60. Hendrix S, Clark A, Nygaard I, Aragaki A, Barnabei V, **McTiernan A**. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J. Obstet Gynecol 2002 Jun;186(6):1160-6.
61. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW, Barrett-Connor E, Birkhauser MH, Brinton LA, Collins A, Collins P, Crosignani PG, Dennerstein L, Ettinger B, Gustafson JA, Guthrie J, Henderson VW, Hendrix S, Klein BEK, LaVecchia C, Lindsay R, Maggi A, McGowan JA, **McTiernan A,** Nilsson S, Redford M, Resnick SM, Rossouw JE, Santoro N, Sherman SS. Executive summary. In International Position Paper on Women's Health and Menopause: a Comprehensive Approach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp. 1-22.
62. LaVecchia C, Brinton L, **McTiernan, A** Hormone replacement therapy, related therapies, and cancer. In International Position Paper on Women's Health and Menopause: a Comprehensive Approach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp.223-250.
63. Barrett-Connor E, Hendrix S, Ettinger B, Wenger NK, Paoletti R, Lenfant CJM, Pinn VW, Birkhauser MH, Brinton LA, Collins A, Collins P, Crosignani PG, Dennerstein L, Gustafson JA, Guthrie J, Henderson VW, Klein BEK, LaVecchia C, Lindsay R, Maggi A, McGowan JA, **McTiernan A,** Nilsson S, Redford M, Resnick SM, Rossouw JE, Santoro N, Sherman SS. Best clinical practices: a comprehensive approach. In International Position Paper on Women's Health and Menopause: a Comprehensive Appoach. Wenger NK, Paoletti R, Lenfant CJM, Pinn VW (eds). NIH Publication No. 02-3284. 2002, pp. 271-288.
64. Byers T, Thun M, **McTiernan A**, Doyle C, et al. American Cancer Society Guidelines for Nutrition and Physical Activity and Prevention of Cancer. CA: Cancer J Clin 2002;52:92-119.
65. Morimoto L, White E, Zhao C, Chlebowski R, Hays J, Kuller L, Lopez AM, Manson J, Margolis K, Muti P, Stefanick M, **McTiernan A**. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative. Cancer Causes and Control. 2002;13:741-751.
66. ^Bossetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, **McTiernan A**, Land C, Mabuchi K, Jin F, Wingren G, Hallquist H, Glattre E, Lund E, Levi F, Linos D, La Vecchia C. A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables. Cancer Causes and Control 2002;13:765-775.
67. LaVecchia C, Brinton LA, **McTiernan A.** Cancer risk in postmenopausal women. Bailliere's Best Practice and Research - Clinical Obstetrics & Gynaecology 2002 Jun;16(3):293-307.
68. Andersen R, Bowen D, Yasui Y, **McTiernan A**. Awareness and concern about ovarian cancer among women at risk due to a family history of breast or ovarian cancer. Clinical Journal of Women's Health 2002;2:5-12. (also reprinted in Am J Obstet Gynecol. 2003 Oct;189(4 Suppl):S42-7.)
69. Bowen D, Burke W, Yasui Y, **McTiernan A**, McLaren D. Effects of risk counseling on interest in genetic testing in lower risk women. Genetics in Medicine 2002; 4:359-365.

70. Evenson K, Wilxox S, Pettinger M, Brunner R, King AC, **McTiernan A**. Vigorous leisure activity through women's adult life: The Women's Health Initiative Observational Cohort Study. American Journal of Epidemiology 2002;156:945-953.

2003

71. Bowen D, Powers D, Anderson R, Burke W, **McTiernan A,** Durfy S, Helmes A. Predicting breast cancer screening with emotion and cognition. Journal of Social and Clinical Psychology 2003;22(2):213-232.

72. ^**Irwin M, Yasui Y, Ulrich CM, Bowen D, Rudolph RE, Schwartz RS, Yukawa M, Aiello E, Potter JD, **McTiernan A**. Effect of exercise on total and intra-abdominal body fat in postmenopausal women: a randomized controlled trial. JAMA 2003;289: 323-330.

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BOOKS

1. **McTiernan A**. *Cured: A Doctor's Journey from Panic to Peace*. Central Recovery Press. February 2021.
2. **McTiernan A**. *Starved: A Nutrition Doctor's Journey from Empty to Full*. Central Recovery Press. November 2016.
3. **McTiernan A**, Gralow J, Talbott L. *Breast Fitness: An Optimal Exercise and Health Plan for Reducing Your Risk of Breast Cancer.* St. Martin's Press, New York. October 2000 (hardcover), October 2001 (softcover)
4. International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention, Vol. 6, Weight Control and Physical Activity, Lyon, IARC Press, 2002 (member of writing group)
5. **McTiernan A.** (Editor) Cancer Prevention and Management Through Exercise and Weight Control CRC Press LLL, 2006.
6. **McTiernan A.** (Editor) Physical Activity, Dietary Calorie Restriction, and Cancer (Energy Balance and Cancer). Springer; 1st Edition. November 19, 2010.

REPORTS, EDITORIALS, BOOK CHAPTERS, LETTERS, AND INVITED REVIEWS

1. **McTiernan A:** Does breastfeeding prevent breast cancer? (editorial) Breastfeeding Abstracts 6:19, 1987.
2. Henderson M and **McTiernan A**. Clinical Programs for Breast Cancer Protection. Reducing Breast Cancer in Women. B. Stoll, ed. The Netherlands. Kluwer Acad. Pub. 177-183, 1995.
3. Chlebowski RT, **McTiernan A**. Hormone Replacement Therapy and Breast Cancer: Limitations of Current Evidence. American Society of Clinical Oncology Education Book (Fall) 1998:87-91.

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5. **McTiernan A.** Cancer Prevention. In Medical and Psychological Aspects of Sport and Exercise. DI Mostofsky and L Zaichkowsky, (eds.) Morgantown, WV, Fitness Information Technology, Inc. 2002
6. **McTiernan A**. Recent Controversies in Mammography Screening for Breast Cancer. Medscape Women's Health eJournal 2002;7(2).
7. **McTiernan A**. Lifestyle Factors in Breast Cancer. Breast Cancer Online. 2003 http://www.bco.org/article.asp?article=105
8. **McTiernan A.** Obesity and Cancer: Potential Management Strategies. American Society for Clinical Oncology Proceedings, 2004.
9. **McTiernan A.** Obesity in the Breast Cancer Survivor. In Nutritional Oncology. Heber D. and Blackburn G. (Eds). San Diego, Academic Press, 2005.
10. **McTiernan A.** Low carb diets: will they be effective in reducing breast cancer risk? American Society for Clinical Oncology Proceedings, 2005.
11. **McTiernan A**. Mechanisms associating physical activity with cancer incidence: exercise and sex hormones. In **McTiernan A.** (Editor) Cancer Prevention and Management Through Exercise and Weight Control CRC Press LLL, 2005.
12. **McTiernan A**. Mechanisms associating physical activity with cancer incidence: intervention studies in humans. In **McTiernan A.** (Editor) Cancer Prevention and Management Through Exercise and Weight Control CRC Press LLL, 2005.
13. Kaaks R and **McTiernan A**. Mechanisms associating obesity with cancer incidence: obesity and sex hormones. In **McTiernan A.** (Editor) Cancer Prevention and Management Through Exercise and Weight Control CRC Press LLL, 2005.
14. **McTiernan A.** Breast Cancer Prevention. Consultant 2006; 46(4): 407-14
15. Ulrich CM, Chubak J, **McTiernan A.** Re: Exercise, vitamins and respiratory tract infections. American Journal of Medicine. [December 2007].
16. **McTiernan A.** Diet, Exercise, and Lifestyle in the Prevention and Recurrence of Breast Cancer. In Sanchez- Basurto C & Sanchez-Forgach ER. Tratado de Enfermedades de la Glandula Mamaria, Mexico City, Mexico, 2007
17. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: U.S. Department of Health and Human Services, 2008. (Member of Committee)
18. Chan D, Thune I, **McTiernan A**. Invited commentary on Chan et al., Body Mass Index and Survival in Women With Breast Cancer–Systematic Literature Review and Meta-Analysis of 82 Follow-Up Studies. Practice Update. http://www.practiceupdate.com/explore/ May, 2014.

MANUSCRIPTS SUBMITTED FOR PUBLICATION

1. **McTiernan A.** Diet Matters in Breast Cancer Prognosis: Clinical Trial Evidence and Questions. Clinical Cancer Research 2023 (invited commentary)

INVITED SCIENTIFIC PRESENTATIONS (does not include conference abstracts)

1. "Women's Health and the Women's Health Initiative." Fred Hutchinson Cancer Research Center, WHI Clinical Center Staff Trainings, 1993-1997.
2. "The Women's Health Initiative: An Overview." University of Washington, Department of Epidemiology Seminars, February 8, 1994.
3. "Risk Assessment for Breast Cancer." University of Washington, Department of Surgery Breast Cancer Conference, April 26, 1994.
4. "Risk Assessment for Breast Cancer." Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994.
5. "Assessing Individual Risk for Breast Cancer." Cancer in Lesbians Symposium, Fred Hutchinson Cancer Research Center, December 2, 1994.
6. "Breast Cancer in High Risk Populations: Women's Health Initiative." Fred Hutchinson Cancer Research Center Scientific Retreat, December 7, 1994.
7. "The Women's Health Initiative." Invited presentation at American Society for Preventive Oncology, Women's Cancers Study Group Meeting, March 11, 1995.

8. "Prevention in Practice and Trials." Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
9. "Exercise and Breast Cancer." Beating Breast Cancer in the '90's: What Everyone Needs to Know about Breast Cancer, University of Washington/Fred Hutchinson Cancer Research Center, April 23, 1996.
10. "Women's Health Initiative." Women's Health Grand Rounds, University of Washington Medical Center-Roosevelt, January 6, 1996.
11. "Exercise and Cancer." Interdisciplinary Cancer Course, Fred Hutchinson Cancer Research Center, March 26, 1997.
12. "Exercise and Breast Cancer." Nutrition Seminar, Department of Nutrition, University of Washington School of Public Health, April 10, 1997.
13. Panel Discussant, "Epidemiologic Issues", NAPBC Workshop on Physical Activity and Breast Cancer, Nov 13-14, 1997.
14. "Diet and Exercise" Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, October 7, 1998.
15. "Exercise and Breast Cancer" American College of Sports Medicine, Seattle, WA, June 2, 1999.
16. "Physical Activity and Reproductive Hormones" Cooper Institute Conference on Physical Activity and Cancer, Dallas, Texas, November 5-7, 2000
17. "Weight Matters in Breast Cancer Prevention and Rehabilitation" Oncology Grand Rounds. Southwest Cancer Center at University Medical Center, Lubbock, Texas, March 2001
18. "Body mass, physical activity, and sex hormones in postmenopausal breast cancer patients". American Cancer Society Science Writers Conference, April 2001
19. "Obesity and Women's Cancer" Keynote Lecture, North American Association for the Study of Obesity, October 2001.
20. "Physical Activity and Breast Cancer ", Women's Sports International, St. Louis, June 2002.
21. "Exercise and Breast Cancer", FHCRC Oncology Grand Rounds, October 2002.
22. "Physical Activity after Cancer: Physiologic Outcomes" in Exercise and the Cancer Survivor: What Should we Recommend?, American Dietetic Association Food and Nutrition Conference and Exhibition, Philadephia, October 2002.
23. ** "Exercise and the Prevention of Colorectal Cancer" European School of Oncology Second Colorectal Cancer Conference, Rome, Italy, October 2002.
24. "Energy Balance – an Etiologic Factor in Human Cancer: Randomized Trial of Exercise Effect on Breast Cancer Biomarkers." Oslo Norway, July 2002.
25. "Exercise and Breast Cancer: Impact on Prevention and Recurrence" The Gibson Lecture in Cancer Prevention Endowed Lectureship, University of Virginia School of Medicine, February 26, 2003
26. "Exercise, Body Fat, and Breast Cancer" Florence Ettelson Memorial Lectureship Medicine Grand Rounds, Providence St. Vincent Medical Center, Portland, OR October 2003
27. "Exercise and Breast Cancer" U. Washington Geriatrics Grand Rounds October 2003
28. "Body Mass Index & Breast Cancer Risk" Challenges & Controversies in Breast Cancer, U Washington School of Medicine CME, October 2003
29. "Diet and Physical Activity" 2nd Emerging Trends in Adjuvant Therapy of Breast Cancer Conference, New York City, October 2003.
30. "Exercise in the Prevention of Breast and Colon Cancer" New England American College of Sports Medicine, November, 2003.
31. "Managing Toxicities of Therapy: Weight Loss and Exercise" School of Breast Oncology, November 2003
32. "Exercise and Breast Cancer Prevention" U. Hawaii, January 2004
33. ** "Obesity and Cancer" 2nd International Conference on the Future of Supportive Therapy in Oncology, St. Kitts, Carribean, February 2004
34. "Exercise and Breast Cancer" University of Alabama at Birmingham, CNRC/Nutrition Sciences Seminar Series, March 2004
35. "WHI Estrogen plus Progestin and Breast Cancer Results" FHCRC Gynecologic Cancer Research Program, March 2004
36. ** "Exercise Effects on Total Body Fat, Intra-Abdominal Fat, Insulin, Leptin, and the Metabolic Syndrome in Menopause" Plenary Session, 5th International Symposium on Women's Health and Menopause, Florence, Italy, April 2005
37. "Exercise and Women's Health" University of Virginia, May 2004
38. "Colon ca, biomarkers, and exercise" American College of Sports Medicine, 2004

39. “Obesity Management in Cancer Patients” ASCO, June 2004
40. ** “Effect of Physical Activity on Breast and Colon Cancer Biomarkers” Ireland/Northern Ireland/NCI Cancer Consortium Seminar on Obesity and Cancer, Dublin, Ireland, September 2004
41. “Exercise Trials in Cancer Prevention” AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
42. “Physical Activity, Endogenous Hormones, and Cancer Etiology” Plenary Session AACR Frontiers in Cancer Prevention, Seattle, WA October 2004
43. “Obesity in Breast Cancer Patients” School of Breast Oncology, Atlanta, Georgia, November 2004
44. “Nutrition, Physical Fitness, and Cancer “ Aultman Cancer Center, Canton, Ohio, November 2004
45. "Effects of Menopausal Hormone Therapy and Tamoxifen on Mammographic Density" University of Virginia, Department of Radiology, Februrary 2005.
46. “Optimizing Health Outcomes” in Oncology Care in the 21st Century: Integrating Care along the Health Care Continuum, Arthur G. James Cancer Hospital Ohio State University, February 2005
47. “Obesity, Exercise, and Breast Cancer”, Tyler, Texas Breast Cancer Conference (talks to oncologists and lay audiences) March 2005
48. “Breast Fitness” talk to women’s health providers, Anchorage, Alaska, May 2005
49. “Low Carb Diets: Will They Be Effective in Reducing Breast Cancer Risk?” ASCO, Orlando 2005.
50. ** “Biologic mechanisms involved in the association between physical activity and cancer: results from recent randomized controlled intervention trials” Eurocancer, Paris, June 2005.
51. ** “Exploring Mechanisms Relating Energy Balance and Cancer” IARC, Lyon, France, June 2005.
52. “Prevention of New and Recurrent Cancers: Lifestyle and Chemoprevention” and “Cancer Screening and Management: The PCP's Role” Issues in Aging Conference, New Orleans, July 2005
53. "Exercise and Cancer Prevention" Rockefeller, NYC, September 2005
54. ** “Open Forum of Breast Health”, Mexico City, Mexico, October 2005
55. “Breast Fitness: Exercise for Breast Cancer Patients and Survivors”, Cancer Wellness Center Northbrook,IL, November 2005
56. “Obesity in Breast Cancer Patients”, School of Breast Oncology, Atlanta GA, November 2005
57. "Insulin Resistance Syndrome and Cancer Risk", International Conference on Metabolic Syndrome, San Francisco, November 2005
58. “Selected Major Findings from the OS Results: Breast Cancer”, WHI Conference, Bethesda, February 2006.
59. “Intermediate Endpoints in Energy Balance and Physical Activity Trials” NCI Workshop on State of the Evidence for a Weight Control Trial to Prevent Breast Cancer, Bethesda, March 2006.
60. “Physical Activity and Cancer Recurrence and Survival”, Symposium: "Physical Activity across the Cancer Continuum" for the CDC International Congress on Physical Activity and Public Health, Atlanta, April 2006
61. “Exercise, Estrogens, and Breast Cancer: Physical Activity Trials” American College of Sports Medicine, May 2006.
62. “Exercise and Nutrition in Chemoprevention” WCRF/AICR International Research Conference, Washington DC, July 2006.
63. ** “Exercise and Cancer Prevention”. National University of Singapore, Singapore, July 2006.
64. ** “Breast Cancer Prevention”, “Lifestyle, Diet, and Breast Cancer ”, “Lifestyle changes may reduce the risk of recurrence” Mexican Association of Breast Diseases 5th Annual Meeting, Leon, Mexico, August 2006.
65. “WHI and Breast Cancer” Seattle Gynecological Society, Seattle, September, 2006
66. "Physical Activity, Weight Control, and Cancer Prevention” Dana Farber Cancer Center Channing Laboratory and Harvard School of Public Health Seminar Series Speaker, October 2006.
67. “Obesity in Breast Cancer Patients”, School of Breast Oncology, Atlanta GA, November 2006
68. “Energy Balance and Cancer: Human Intervention Studies” NCI Energy Balance Working Group, Bethesda, MD, January 2007
69. “Overweight, Obesity, and Sedentary Lifestyle in Breast Cancer Prognosis”. Interdisciplinary Science, Health Promotion, and Disease Prevention. Pasadena, CA. May 2, 2007.
70. “Transdisciplinary Research to Elucidate the Pathways Linking Components of Energy Balance to the Cancer Process” Transatlantic Research and Innovation Symposium. Research Triangle Park, North Carolina, May 3, 2007.
71. “Obesity, Physical Activity, & Breast Cancer” University of Washington CNRU May 11, 2007
72. “Women’s Health Initiative Clinical Trials” Northwestern University Clinical Research Educational Conference, Chicago, May 18, 2007.
73. “Exercise and Weight Loss in Women and Men” Northwestern University Dept of Preventive Medicine, May 18, 2007.

74. FASEB Energy Balance, Body Fat & Disease, "Exercise and Cancer Prevention", and chair of session "Exercise and Cancer Prevention & Prognosis" Indian Wells, CA, August 2007
75. MD Anderson Cancer Prevention Grand Rounds, "Overweight, Obesity, Physical Activity, and Breast Cancer Prevention" Houston, Sept 2007
76. MD Anderson Integrative Medicine Program Lecture Series talk "Obesity, Weight Loss, and Physical Activity for Cancer Patients and Survivors" Houston, Sept 2007
77. **Breast Health Global Initiative "Primary prevention of breast cancer: lifestyle changes, diet, western lifestyle", Budapest, Hungary, October 2007
78. "Obesity in Breast Cancer Patients", School of Breast Oncology, Atlanta GA, November 2007
79. "Breast Cancer: Women at Risk and New Strategies for Prevention", Practicing Clinicians Exchange, San Francisco, CA November 2007
80. "Exercise Effect on Inflammation and Other Cancer Biomarkers", Southeast ACSM, Birmingham, AL, February 2008
81. "Professional Development for Women", Southeast ACSM, Birmingham, AL, February 2008
82. "Exercise and Body Composition Change Effects on Sex Hormones in Postmenopausal Women", AACR – TREC Markers & Mediators, Virginia, February 2008
83. "Obesity in Breast Cancer Risk and Prognosis", Case Western University, Cleveland, OH, March 2008
84. "Exercise Interventions in Breast Cancer Prevention and Outcomes", Cleveland, OH, March 2008
85. "TREC Talk", Cancer Prevention and Research Center Retreat, Coeur d' Alene, ID, March 2008
86. ** "Fitness vs. Fatness: Evidence from Epidemiologic and Intervention Studies on the Separate and Combined Effects of Physical Activity and Obesity on Cancer Risk", International Physical Activity Meeting, Amsterdam, April 2008
87. "Influence of Exercise on Immune Function: Possible Link to Breast Cancer", ACSM, Indianapolis, May 2008
88. "Breast Cancer Prevention and Survivorship through Lifestyle and Chemoprevention", Memorial Sloan Kettering Cancer Center, New York City, NY, September 2008
89. ** "Early Detection, Diet, Physical Activity, and Cancer", Women in High Places meeting, Riyadh, Saudia Arabia, October 2008
90. **"Diet and Breast Cancer", Saudi Arabian Cancer Conference, Riyadh, Saudia Arabia, October 2008
91. "Physical Activity & Weight Control in Breast Cancer Prevention & Prognosis", Alaska Conference: "Reducing the Risk, Advancing the Cure: New Recommendations, New Options for Primary Care Providers and Survivors." Televised from Seattle, October 2008
92. "Lessons Learned from Real-Life Lifestyle Interventions", The Obesity Society, Phoenix, AZ, October 2008
93. "Breast Cancer: Weight Loss and Exercise", School of Breast Oncology, Atlanta, GA, November 2008
94. "Fitness vs. Fatness in Breast Cancer Risk and Prognosis", Frontiers of Cancer Prevention, Washington, DC, November 2008
95. "Effects of Exercise and Obesity on Inflammation and Cancer Risk", University of Washington, DERC Seminar Series, February 2009
96. "Does Weight Loss Reduce Cancer Risk?" The Obesity Society, October 2009.
97. Roger E. Moe Award for Translational Research Lecture "Effects of Weight and Physical Activity on Breast Cancer Prognosis" University of Washington *Current Concepts and Challenges in Breast Cancer* October 2009
98. "Lessons learned from physical activity (exercise) interventions" AICR Annual Research Conference on Food, Nutrition, Physical Activity and Cancer, Washington, DC, November 2010
99. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2010
100. "Transdisciplinary studies of weight loss and exercise interventions in women at increased risk for breast cancer", AACR, Washington, DC, April 2010
101. "Exercise Effects on Breast Cancer Biomarkers", International Society for Behavioral Nutrition & Physical Activity, Minneapolis, MN, June 2010
102. **"Physical Activity & Cancer" Lecture, Helsedirektoratet (Directory of Health), Oslo, Norway, December 2010
103. "Physical Activity, Weight Control and Cancer Prevention" Physical Activity and Nutrition seminar series University of Michigan. The School of Kinesiology, February 2011.
104. "Physical Activity in Cancer Prevention" American College of Sports Medicine President's Talk, Denver, CO, June 2011
105. "Breast Cancer Prevention" Foundation for Care Management, Lakewood, WA, January 2011
106. "Breast Cancer Prevention" Foundation for Care Management, Coupeville, WA, February 2011
107. "Inflammation, Insulin, & Obesity in Breast Cancer Survival", University of Texas Southwestern Medical Center, Dallas, Texas, September 2011

108. "Interventions in cancer survivors; issues and challenges in this population", Institute of Medicine Workshop "The Role of Obesity in Cancer Survival and Recurrence", Washington, DC, October 31-November 1, 2011
109. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2011
110. **"Obesity, Physical Activity, & Related Mechanisms in Breast Cancer Survival", Norwegian Congress in Oncology, Oslo, Norway, November 2011
111. "Impact of Obesity on Cancer "Swedish Hospital Medical Center CME, Seattle, WA May 2012
112. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials", University of Hawaii, July 2012
113. "The Impact of Intentional Weight Loss on Cancer Risk", The Obesity Society, San Antonio, Texas, September 2012
114. "Dietary Weight Loss and Exercise Effects on Metabolic Hormones in Postmenopausal Women", Fred Hutchinson Cancer Research Center Symposium on Metabolism and Cancer, September 2012
115. **"Lifestyle Modifications to Reduce Cancer Risk and Improve Overall Health", Global Summit on International Breast Health, Vienna, Austria, October 2012
116. **" Medical Perspective on the Influential Role of Obesity in the Risk and Prognosis of Breast Cancer" and "Obesity, chronic diseases and cancer, a common link with lifestyle" Mexican Association of Mastology, Villahermosa, Tabasco, Mexico, October 2012
117. "Effects of Weight Loss and Physical Activity on Cancer Risk Factors: Evidence from Randomized Trials" Oregon Health Sciences University, October 2012
118. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2012
119. "Dietary weight loss and exercise effects on metabolic and sex hormones in postmenopausal women." American Association for Cancer Research, Washington, DC, April 2013
120. "Obesity, Weight Loss, Vitamin D, and Cancer Biomarkers" Fred Hutchinson Cancer Research Center Joint Cancer Prevention/Epidemiology Seminar Series, May 2013
121. **"The WCRF/AICR Continuous Update Project – Systematic Reviews on Nutrition, Physical Activity & Health Outcomes in Cancer Survivors" International Union of Nutrition Scientists (IUNS) 20th International Congress of Nutrition, Granada, Spain, 2013
122. **"Appraisal of Evidence for Obesity Effects on Cancer" IASO/WCRF Obesity, Physical Activity and Cancer, London, 2013
123. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers" University of Illinois Symposium, Chicago, October 2013
124. **"Obesity, Physical Activity and Cancer" State Institute of Diabetes and Endocrinology & Catholic University Post Graduation course on Endocrinology and Metabolism. Rio de Janeiro, Brazil, October 2013
125. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2013
126. "Obesity, Physical Activity and Cancer" Keynote Speaker, The Center for Energy Balance in Cancer Prevention & Survivorship Research Retreat, MD Anderson Cancer Center, February 2014
127. **"Exercise in Cancer Prevention & Survivorship", Athens Institute for Education and Research, 10th Annual International Conference on Kinesiology and Exercise Sciences, Athens, Greece, August 2014
128. **"Weight Loss & Exercise Effects on Cancer Biomarkers," University of Tromso, Norway, September 2014
129. "Breast Cancer Survivors: Findings from the Continuous Update Project," American Institute for Cancer Research Annual Conference, October, 2014.
130. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2014
131. "Obesity, Weight Loss, & Breast Cancer," University of Iowa Diabetes and Obesity Talks Seminar Series, November, 2014
132. "Weight Loss & Exercise Effects on Breast Cancer Biomarkers," Memorial Sloan Kettering Cancer Center, New York, February, 2015.
133. "Physical Activity & Weight Loss Effects on Cancer Biomarkers", NCI Schatzkin Talk, May 2015
134. "Obesity, Weight Loss, Exercise & Breast Cancer" Seattle Cancer Care Alliance, May 2015
135. **"Associations of Weight, Physical Activity, & Diet with Breast Cancer Survival", International Society for Behavioral Nutrition & Physical Activity, Edinburg Scotland, June 2015
136. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2015
137. **"The role of physical activity on cancer risk: epidemiology & molecular mechanisms" WCRF International and World Obesity Federation Joint Conference, September 2016
138. **"Anthropometry: What Can We Measure & What Does It Mean?" WCRF International and World Obesity

Federation Joint Conference, September 2016
139. ""Exercise, Weight, and Cancer Risk" University of Alabama Center for Exercise Medicine, Birmingham, September 2016
140. **"Long-term Effects of Exercise & Weight on Breast Cancer Biomarkers" University of Tromso, Norway, October 2016
141. "Exercise, Weight, and Cancer Risk" Roswell Park Prevention Grand Rounds, Buffalo, NY, October 2016
142. "Modifiable Health Behaviors for Cancer Survivors // Health Promotion: Exercise, Physical Rehab" SCCA Cancer Survivorship for Physicians CME, October 2016
143. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2016
144. "Physical Activity & Cancer – What We Know, What We Don't Know" American Institute for Cancer Research AICR's 25th Research Conference, November 2016
145. **"Screening for Breast Cancer: Pro", EuroMedLab, Athens, Greece, June 2017
146. **"Weight Control and Exercise for Breast Cancer Pts & Survivors", Mexican Association of Mastology, 14th National Congress, Guadalajara – México, August, 2017
147. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2017
148. **"Effects of Weight Loss on Cancer Biomarkers," Canadian Cancer Research Conference, Vancouver, BC, Canada, November 2017
149. "Physical Activity and Diet for Cancer Prevention and Treatment: State of the Evidence," Arizona State University, Tempe, Arizona, February, 2018
150. "Physical Activity for Cancer Prevention and Treatment: State of the Evidence," Wolffe Lecture, American College of Sports Medicine, May 2018
151. ** Diet, Weight & Exercise in Cancer Prevention & Survival: the World Cancer Research Fund Report," Oncology Grand Rounds, BC Cancer, Vancouver, BC, Canada, September 2018
152. **"Physical Activity and Cancer Prevention," National Center for Sport and Exercise Medicine, University of Loughborough, England, July 2018
153. "Weight Control and Exercise for Breast Cancer Prevention," National Cancer Institute, Stars in Nutrition and Cancer lecture, October, 2018
154. "Weight Control and Exercise for Breast Cancer Prevention" The Ohio State University Comprehensive Cancer Center, January 2019
155. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2018
156. "Talcum Powder Products and Ovarian Cancer," appearance before Congress of the United States, House of Representatives, Subcommittee on Economic and Consumer Policy Hearing on Examining the Public Health Risk on Carcinogens and Consumer Products, March 2019
157. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2019
158. **"Physical Activity for Cancer Prevention & Treatment: Keynote Talk," Canadian Society for Exercise Physiology, Kelowna, BC, Canada, November 2019
159. "Weight Loss & Exercise for Breast Cancer Survivors" Breast and Ovarian Cancer Translational Incubator, Fred Hutchinson, UW Medicine, Seattle Cancer Care Alliance, August 2020
160. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2020 (virtual)
161. "Weight Control and Exercise for Breast Cancer Prevention & Prognosis" Jean Andrews Centennial Visiting Professorship in Human Nutrition, University of Texas, Austin, April 2, 2021 (virtual)
162. "What Do Weight and Exercise Have to Do with Breast Cancer?" Jean Andrews Centennial Visiting Professorship in Human Nutrition, University of Texas, Austin, April 3, 2021 (virtual)
163. "Cancer Biomarker Changes in Weight Loss Studies: Prevention" Trans-NIH Consortium: RCTs of Lifestyle Weight Loss Interventions for GWAS. August 26-27, 2021 (virtual)
164. "Weight Loss Effects on microRNA Related to Breast Cancer and Obesity" Breast Cancer Research Foundation Annual Scientific Meeting, October, 2021 (virtual)
165. "Weight Loss and Exercise" School of Breast Oncology, Atlanta GA, November 2021 (virtual)
166. "Weight, Physical Activity and Cancer Prevention" Grand Rounds, University of Washington, School of Medicine, Division of Gerontology & Geriatric Medicine, April 15, 2022 (virtual)
167. "Physical Activity and Nutrition," Implementing Clinic-Based Cancer Prevention Strategies, National Academies (Medicine) National Cancer Policy Forum workshop, *Advancing Progress in Cancer Prevention and Risk Reduction.* June 27-28, 2022 (virtual)

168. "Exercise Before and During Cancer Treatment," NIH Pathways to Prevention Workshop, *Nutrition as Prevention for Improved Cancer Health Outcomes*, July 26-28, 2022 (virtual)
169. "Acute Exercise in Women with Breast Cancer Study – ACE2," Breast Cancer Research Foundation Play for Pink, November 10, 2022 (virtual)

** International Presentations

FUNDED RESEARCH PROJECTS (total dollars unless otherwise noted)

Completed

- A Case-Control Study of Thyroid Cancer in Women, **PI: Anne McTiernan**, American Cancer Society Institutional Grant 1N-26-U, 1979-1982.
- Counseling Strategies for Breast Cancer Risk, PI: Deborah Bowen, PhD, NIH Grant #HG/CA01190-01, 1994-97, $654,409.00.
- Fenfluramine as an Adjunct to Smoking Cessation Therapy, PI: Deborah Bowen, PhD, NIH Grant #R29CA50858, 1990-94.
- Feasibility Study of an Exercise-Diet Program for Breast Cancer Patients, PI: Anne McTiernan, FHCRC Bid and Proposal funds, 1995-1996, $10,000 (direct)
- Echocardiographic Follow-up to a Randomized Trial of Fenfluramine in Women Smokers, PI: Deborah Bowen, PhD, Wyeth Ayerst research contract, 1998, $1,957,627.
- A Randomized Controlled Trial of Fat Reduction and Risk of Proliferative Forms of Benign Breast Disease, WHI Ancillary Study, PI: Tom Rohan, MD; **PI of FHCRC subcontract to U. Toronto: Anne McTiernan,** $13,699.
- Effect of Exercise on Mammogram Densities, **PI: Anne McTiernan,** FHCRC Bid and Proposal funds, 1999-2000.
- SEER Special Studies RFP Interaction of Genetic Susceptibility and Hormonal Exposures in Breast Cancer Prognosis, **PI: Anne McTiernan,** 1999-2001, $137,465.
- SEER Special Studies RFP Mammographic Breast Density and Breast Cancer Prognosis, **PI: Anne McTiernan,** 1999-2001, $123,558.
- Genetic Risk Information for a Defined Populations, PI: Deborah Bowen, PhD, NIH grant #HG/CA1190-01, 1998-2001, $1,143,890.
- Effect of Hormone Replacement Therapy on Mammographic Density, WHI Ancillary Study, PI: Barbara Hulka, MD, MPH; **PI of FHCRC subcontract to UNC Chapel Hill: Anne McTiernan,** 1998-2003, $876,824.
- Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan,** NIH R01CA/AG69334-01A2, 1997-2003, $1,562,811.
- Effect of Exercise on Immune Function in Postmenopausal Women: Supplement to Effect of Exercise on Sex Hormones in Postmenopausal Women, **PI: Anne McTiernan,** NIH R01CA/AG69334-01A2, 1998-2003, $439,112.
- Women's Intervention Nutrition Study (WINS) FHCRC Clinical Center, PI: Alan Kristal; Past-PI, $28,400.
- Exercise Intervention Trial for Colorectal Polyp Patients, **PI: Anne McTiernan,** R01 CA77572-01, 2000-2007, $4,046,212.
- Clinical Coordinating Center, Women's Health Initiative Trial & Observational Study, PI: Ross Prentice; **Role on project: Co-Investigator**, NIH N01-WH-2-2110, 1992-2007+, $112,336,577.
- Randomized, Double-Blind, Placebo Controlled Trial of 4-OH Tamoxifen Gel in Premenopausal Women with 50-80% Density in Breast tissue Based on Digitized Analysis of Screening Mammography, Besins International U.S. Inc. **PI: Anne McTiernan,** 2002-2003, $116,165.
- Seattle Cancer & Aging Program – Pilot: Effect of Exercise on Prostate Cancer Biomarkers: An Ancillary Study to a Randomized Controlled Clinical Trial, PI: Peter Rabinovitch; **PI of Pilot Study: Anne McTiernan**, P20 CA103728, 2004-2006, $39,049.
- Study of Tamoxifen vs. Raloxifene (STAR), PI: R. Clarfeld; **Role on project: Co-Principal Investigator.**
- Exercise and Fitness in Childhood Cancer Survivors, PI: Debra Friedman; **PI of FHCRC Subcontract: Anne McTiernan,** NCI R21, 2004-2006, $23,904 (direct).
- Proteomic Markers of Health Behaviors, PI: Paul Lampe/Yutaka Yasui; **Role on project: Co-Investigator**, NCI-5 R03 CA108339-02, 2004-2006, $173,000.

- Randomized placebo-controlled biomarker modulation trial using Celecoxib in premenopausal women at high risk for breast cancer, SWOG, PI: Powell Brown; **PI of FHCRC subcontract: Anne McTiernan**, NIH/NCI CA37429, 2005-2006, $37,799.
- Effects of Aspirin on Biomarkers of Breast Cancer Risk (Avon Progress for Patients Funds), PI: Nicole Urban**; Role on project: Project Leader, wrote proposal and directed trial**, 2004-2007, $496,238.
- ALPHA Trial: Alberta Physical Activity and Breast Cancer Prevention Trial. Canadian Breast Cancer Research Initiative, PIs: Christine Friedenreich and Kerry Courneya; **Role on project: Co-Investigator**, 2002-2007, $1,104,147.
- Mammographic Density and Invasive Breast Cancer, PI: Etta Pisano, **PI of FHCRC Subcontract: Anne McTiernan**, R01 CA105007-01, 2004-2007, $50,524 (direct).
- Cognitive Effects of Aerobic Exercise for Adults with Impaired Glucose Tolerance: A Controlled Trial (American Diabetes Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Cognitive Effects of Aerobic Exercise for Adults with Mild Cognitive Impairment: A Controlled Trial (Alzheimer's Association), PI: Laura Baker; **Role on project: Co-Investigator**, 2004-2007.
- Social and Physical Activity of Childhood Cancer Survivors, PI: Debra Friedman; **Role on project: Co-Investigator**, NIH/NCI CA 104123-01A2, 2005-2007, $107,500.
- UW Multidisciplinary Research Training Grant, PI: R Deyo; Role on project: **Co-Investigator, Mentor**, 1 K12 HD 49100-01, 2004-2009, $1,172,239.
- Epidemiology of Gallbladder Sludge and Stones in Pregnancy, PI: Sum Lee; **Role on project: Co-Investigator**, RO1 DK46890, 2003-2008, $372,840.
- Breast Cancer Prognostic Factors/Pathobiology by Age, PI: Kathi Malone; **Role on project: Co-Investigator**, NCI-1 R01 CA098858-01A2, 2004-2009.
- Seattle TREC Center, **PI: Anne McTiernan,** NIH/NCI U54 CA116847, 09/23/2005 – 08/31/2011, $12,612,045.
- Exercise, Diet, and Postmenopausal Sex Hormones, **PI: Anne McTiernan,** NIH/NCI R01 CA105204**,** 09/01/2004 – 06/30/2011, $3,348,605.
- Reducing Obesity at the Workplace: A Randomized Trial, PI: Shirley Beresford; **Role on project: Co-Investigator**, NIH/NHLBI R01 HL079491, 7/1/2004-6/30/2011.
- Effect of Exercise and Weight Loss on Adipose Tissue Biology, **PI: Anne McTiernan**, NIH/NCI R21 *CA131676*, 05/01/2008 – 04/30/2011, $435,600.
- Effect of Dietary Intervention on Insulin and IGF-1 Receptors in Prostate Cancer (Pacific NW Prostate SPORE pilot project), **PI: Anne McTiernan**, NIH/NCI P50 CA97186, 09/01/2009 – 08/31/2011, $48,836.
- Alberta Physical Activity (ALPHA) and Breast Cancer Prevention Trial: an ancillary study examining androgens, biomarkers of obesity, and inflammation. Alberta Breast Cancer Research Initiative, PI: CM Friedenreich; **Role on project: Co-Investigator**, $170,000.
- Bid & Proposal Funds to Assess Baseline Body Composition, by Dual X-ray Absorptiometry (DXA), in Participants of an Ongoing Clinical Trial (Vitamin D, Diet & Activity Study, ViDA) **PI: Anne McTiernan,** 12/1/2010 – 06/30/2011, $16,000 (direct).
- A Phase III Randomized Controlled Study of Exemestane Versus Placebo in Postmenopausal Women at Increased Risk of Developing Breast Cancer. **PI of FHCRC Clinic: Anne McTiernan**, National Cancer Institute of Canada**,** 10/2004 – 11/2012, $1,631,150.
- Komen Scientific Advisory Council Award "Vitamin D, Weight Loss, and Breast Cancer Biomarker," **PI: Anne McTiernan,** SAC110024, 07/01/2010 – 06/30/2012, $500,000.
- Weight Loss & Exercise Effects on Telomere Length in Postmenopausal Women, **PI: Anne McTiernan,** NIH/NCI R21 CA155823**,** 12/14/10 – 11/30/12, $428,705.
- Oxidative Stress in Chronic Kidney Disease, University of UW PI: Jonathan Himmelfarb; **Role on project: PI of FHCRC subcontract**, NIH/NHLBI R01 HL070938, 01/01/2011 – 12/31/2012, $197,630 (FHCRC only).
- Komen Scientific Advisory Council Award "Vitamin D, Weight Loss, and Breast Cancer Biomarker," **PI: Anne McTiernan,** SAC110024, 07/01/2012 – 06/30/2013, $225,000.
- NCI: Exercise Effects on Serum Biomarkers of Angiogenesis, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, NIH/NCI R03 CA152847, 04/01/2011 – 03/31/2013, $176,000.
- HEAL Follow-up, NIH/NCI Contract. Manuscript Development for the HEAL Study of Breast Cancer Prognosis, **PI: Anne McTiernan,** NCI contract, 10/2012-9/201/3

- Vitamin D Effect on Body Composition During Behavioral Weight Loss in Women, **PI: Anne McTiernan**, NIH 1R03CA162482, 04/01/12 – 03/31/14, $175,000
- Effect of Vitamin D and Weight Loss on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/13-9/30/14, $230,378.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/14-9/30/15, $250,000.
- Weight Loss & Cancer Biomarkers in Women: Oxidative Stress & Inflammation, **PI: Anne McTiernan**, NIH/NCI, 1R01CA161131, 04/15/2012 – 9/30/2015, $863,179.
- Safeway Foundation Assessing Vitamin D, Weight Loss and Breast Cancer Risk Factors, Safeway Foundation, PI: Catherine Duggan, PhD; **Role on Project: Co-Investigator & Mentor**, 7/1/2013 – 6/30/2014, $36,000 (in NCE).
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/15-9/30/16, $250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/16-9/30/17, $250,000.
- Methods for Measurement Error in Physical Activity & Diet, PI: CY Wang; **Role on Project: Co-Investigator,** NIH/NHLBI R21HL121347, 12/1/13-12/31/16, $494,493.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/17-9/30/18, $250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/18-9/30/19, $250,000.
- Impact of an exercise program in cancer patients on chemotherapy treatment, **PI's: Anne McTiernan** & Blair Irwin, Ben Greer SCCA Pilot Study Funds, 9/17-8/18, $50,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/19-9/30/20, $250,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/20-9/30/21, $175,000.
- INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A Multicenter, Randomized, Controlled, Phase III Study, PI: Jonathan Wright; **Role on Project: Co-Investigator,** Movember, 2016 –2021
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan**, NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/20, $421,080
- Exercise Effects in Men & Women on Colon DNA Methylation, **PI: Anne McTiernan,** NIH/NCI 1R21CA209203-01A1, 3/15/17 – 2/28/20, Administrative supplement, $176,000
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/21-9/30/22, $190,000.
- The effects of moderate exercise on distress, quality of life, and biomarkers of angiogenesis and chronic stress in ovarian cancer survivors, NCI R21CA215662-01A1, 9/5/2018 – 8/31/2020, PI: Kathryn Pennington; **Role on Project: Co-Investigator** (in no-cost extension)
- An AHEI Dietary Intervention to Reduce Pain in Women with Endometriosis, R01 NR017951-01A1, 2/11/2019 – 12/31/2022, PI: Holly Harris; **Role on Project: Co-Investigator**
- Joint Modeling of Longitudinal Physical Activity and Diet Data and Survival, R21 CA215674-01, 2/2020-1/2022, PI: CY Wang; **Role on Project: Co-Investigator**
- Longitudinal Weight Data from Two Behavioral Weight Loss Randomized Controlled Trial, **PI: Anne McTiernan**, FHCRC Bid & Proposal Funds, 10/17-9/18, $15,000.

Active

- Telephone delivered acceptance and commitment therapy for weight loss, R01 DK124114, 7/1/2020-6/30/2025, PI: Jonathan Bricker; **Role on Project: Co-Investigator**
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, "Exercise-Stimulated Signaling Pathways Associated with Cancer Development and Progression", **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/22-9/30/23, $225,000.
- Effect of Weight Loss & Exercise on Biomarkers of Breast Cancer Risk, "Exercise-Stimulated Signaling Pathways

Associated with Cancer Development and Progression", **PI: Anne McTiernan**, Breast Cancer Research Foundation, 10/1/23-9/30/24, $225,000.

Pending

TEACHING/MENTORING

Junior Faculty

Kathryn Pennington, MD (School of Medicine, OB/GYN, University of Washington)
Holly Harris, PhD (Epidemiology Program, PHS, FHCRC)
Catherine Duggan, PhD (Epidemiology Program, PHS, FHCRC)
Blair Irwin, MD (Multi-Care, Tacoma, SCCA affiliate)
Jonathan Wright, MD, MPH (School of Medicine, Urology, University of Washington & Epidemiology Program, PHS, FHCRC)

Postdoctoral Fellows

1. Melinda Irwin, PhD (current Professor, Epidemiology, School of Public Health Associate Dean of Research, Yale University)
2. Melanie Palomares, MD, MPH (current Senior Medical Director, Exact Sciences, Redwood City, California)
3. Laura Frank, PhD (current Alexion Pharmaceuticals, Inc.)
4. Page Abramson, PhD
5. Karen Foster-Schubert, MD (current Associate Professor, Endocrinology, U. of Washington)
6. Kristin Campbell, PhD (current Professor, Associate Head Research, Physical Therapy, U. British Columbia)
7. Lisa Cadmus-Bertram, PhD (current Associate Professor, Kinesiology, University of Wisconsin-Madison)
8. Ikuyo Imayama, MD (current Assistant Professor, Pulmonology, University of Illinois, Chicago)
9. Caitlin Mason, PhD

Additional Postdoctoral Fellows Working with My Studies' Data

10. Jean De Dieu Tapsoba, PhD (Staff Scientist, FHCRC; primary mentor, CY Wang, PhD)
11. Aaron Thrift, PhD (primary mentor, T. Vaughan, MD)

PhD Committees and Predoctoral Trainee Mentoring

1. Lisa Godefroy Johnson (member of PhD committee, current Staff Scientist, FHCRC)
2. Shelley Slate Tworoger (member of PhD committee, current Associate Center Director of Population Science & Senior Member Moffitt Cancer Center, Tampa, Florida)
3. Cara Frankenfeld (member of PhD committee, current Program Director for the Master of Public Health Program at the University of Puget Sound)
4. Victoria M. Chia (member of PhD committee, current Amgen)
5. Lori Williams (member of PhD committee)
6. Angela Kong, PhD (co-chair of PhD committee, current Assistant Professor University of Illinois, Chicago)
7. Babbette Saltzman (member of PhD committee, current research data analyst, Seattle Childrens Medical Center)
8. Anita Iverson, PhD (visiting Norwegian predoctoral student 2009-10, advising)
9. Adriana Villasenor, PhD (member of PhD committee, current faculty University of California San Diego)
10. Sissi Espetvedt Finstad, MD (Norwegian PhD student, advising)

MS and MPH Committees

1. Margaret Krieg, MD (member of MPH committee)
2. Sylvia Young, MD (chair of MPH committee)
3. Jana Pruski (chair of MPH committee)
4. Melanie Palomares, MD (chair of MPH committee)
5. Susan Stanford (member of MPH committee)
6. Melinda Irwin, PhD (chair of MPH committee)
7. Andrew Shors, MD (member of MPH committee)
8. Libby Morimoto (member of M.S. committee)
9. Breanna Mitchell (member of M.S. committee)

10. Erin Aiello (chair of MPH committee; current Manager, Collaborative Science, Kaiser Permanente Washington Health Research Institute, Seattle)
11. Erin Shade (member of M.S. committee)
12. Julie Meyers (member of M.S. committee)
13. Manish Mohanka, MD (chair of MPH committee; current Associate Professor in UT Southwestern Medical Center, Pulmonary)
14. Vivian Hawkins, PhD (chair of MPH committee; current Epidemiologist in the Washington State Department of Health Office of Communicable Disease Epidemiology)
15. Isaac Rhew, PhD (member of MPH committee; current Research Associate Professor, Psychiatry and Behavioral Sciences, University of Washington)
16. Ann Ready (member of MPH committee)
17. Alanna Boynton (member of MS committee)
18. Heather Hildebrant (member of MPH committee)
19. Jo Henderson (chair of MPH committee)
20. Laura Hooper (member of MPH committee)
21. Kristen Sipsma (member of MPH committee)
22. Karen Foster-Schubert (chair of MS committee; current Associate Professor, Endocrinology, U. of Washington)
23. Winnie Yeung (member of MPH committee)

Advising: Medical Students Research (University of Washington ISMS): Jennifer Rupert, Erin Griffith, Kelley D. Pratt, Maegan Ashworth
Post-Graduate Physician Training in Cancer Prevention & Control (FHCRC): Elliott Rosenberg, MD, MPH, Mary Ann Gilligan, MD, MPH, Maureen Brown, MD
Formal Career Development Mentoring: Karen Foster- Schubert, MD, University of Washington NIH K-12 Fellow 2005-2010; Karen Mustian, PhD University of Rochester NCI Cancer Control Clinical Research Training Program 2004-
FHCRC scientists mentoring: Neli Ulrich, PhD, Rebecca Rudolph, MD, MPH, AnneClaire DeRoos, PhD, Alyson Littman, PhD, Jonathan Wright, MD, MPH, Catherine Duggan, PhD, Larissa Korde, MD
Individual Study Credits

Course	Title	Credits	Years
Epi 499	Undergraduate Research	Var	1997-2005
Epi 600	Graduate Study/Research	Var	1997-2005
Epi 700	Masters Research	Var	1998-2005
Cancer Epi	guest lecture	1999, 2002-2005	

Continuing Medical Education Teaching

- Breast Cancer in Young Women, University of Washington Continuing Education Conference, August 6, 1994, Depts. of Surgery and Medicine.
- Current Concepts in the Early Detection of Breast Cancer, Multicare, Madigan Army Medical Center, and American Cancer Society 3rd Annual Oncology Conference, April 11, 1995.
- Current Concepts in Breast Cancer – 1997, University of Washington Continuing Medical Education, October, 1997, 1999, 2000 (session moderator), 2001, 2003, 2009, 2010
- "Update to the Women's Health Initiative" March 18, 2001, University of Washington talk to IM, GYN, FM residents.

Clinical Teaching (U. of Washington School of Medicine)

- Attending Physician, Adult Medical Center, Harborview Medical Center, 1992-95 – supervised internal medicine residents in primary care setting.
- Mentoring and training geriatric fellow, Dr. Michi Yukawa, in exercise tolerance testing and testing VO2 max (1999)

Other Academic

- Primary Opponent, PhD Thesis Defense, Aina Emaus, University of Oslo, Norway (thesis chair, Inger Thune) 2009

FHCRC SERVICE

- Director, Prevention Center Shared Resource, 2001-2012

- Chair or Member of several faculty promotion committees and 5-year review committees (including 3 within the past year)
- Reviewer for CCSG renewal: 2013, 2018
- Member, Cancer Consortium Scientific Review Committee 2015, 2018
- Member, Scientific Advisory Committee for the Seattle Cancer Care Alliance Prevention Clinic
- Member, Research Trials Office Oversight Committee, 2003 – 2005
- Member, Fred Hutchinson Cancer Research Center Institutional Review Board, 1984-5; 2002 - 2003
- Member, FHCRC Health Care Task Force, 1996
- Member, Clinical Protocol Scientific Review and Monitoring Committee, 1996- 1997
- Organizer, FHCRC Public Health Sciences Hormone Special Interest Group 1995-96
- Member, Seattle Breast Cancer Program Executive Committee, 1998 - 2000
- Member, Ad-Hoc Committee on Improvements in Public Health Sciences Procedures, 1998
- Member, CSS Advisory Committee, 1999 – 2000
- Nutritional/Hormonal Biomarkers group, 2001 – 2002
- Member, CDS Users Group, 2001 – 2002

UNIVERSITY OF WASHINGTON SERVICE

- Reviewer, Royalty Research Fund, Spring, 1997
- U. Washington Breast Cancer Update 2000 Continuing Medical Education – session moderator

PROFESSIONALLY-RELATED COMMUNITY SERVICE

- Medical Advisory Board, Team Survivor Northwest 1997-
- Professional Advisory Committee, Breastcancer.org, 2003-

LAY AUDIENCE PRESENTATIONS

- National Council of Jewish Women, Seattle Section, “Women’s Health Initiative”, Nov 1992
- Nordstrom’s “Face of Breast Cancer” breast cancer awareness seminar, October 1997
- Danskin Women’s Triathalon, 8/15/98
- Afternoon of Hope, Horizon of Hope National Charity Campaign, Longaberger Co., FHCRC, 8/29/98
- Media roundtable, Women’s Health Initiative, December, 1995
- Breast Cancer Forum: Clinical Implications of Current Research, FHCRC, 10/8/98
- Women’s Health Issues Panel, The Healthy Living Expo, Seattle, WA, 2/7/99
- Virginia Mason Hospital Breast Cancer Support Group “Weight Control and Cancer Survival” September 1999.
- FHCRC Volunteer Conference “Breast Cancer Risk Factors” May 2000.
- FHCRC Women’s Health Series “Exercise and Breast Cancer” April 2000.
- Bellevue Rotary Club, “Exercise and Breast Cancer” October 2000.
- Cardio Pulmonary Rehabilitation InstituteOncology Rehabilitation, Lubbock Texas, “Exercise for Breast Cancer Prevention and Rehabilitation”, March 2001
- Greater Cincinnati Breast Cancer Association, October 2001.
- FHCRC Community Lecture "Exercise for Breast and Colon Cancer Prevention" November 2001
- Providence/St. Vincent Medical Center, Portland, OR October 2003
- Women’s Health Day, Anchorage, Alaska 2005
- Cancer Wellness Center, Northbrook, IL 2005
- Additional lay audience talks yearly

MEDIA

- Media (TV) interviews on physical activity, obesity, vitamin D, sleep, cancer: Today Show (NBC); MSNBC News Show; ABC News w/Peter Jennings; ABC World News Tonight; CBS Evening News; CBS News; Seattle KOMO, KIRO, KING, FOX13; WZTV-FOX, KOCO-ABC, WFLA-NBC, WBTV-CBS, WLUK-FOX
- Media (radio): KJZZ, Canadian health radio talk show; numerous Seattle-area radio interviews

- Media (print) –Prevention Magazine, American Health Magazine, Time Magazine, Parents' Magazine, Family Circle, Associated Press, Time, Women's World, Cosmopolitan, Glamour, Self, Reader's Digest, New York Times, Wall Street Journal, LA Times, Parade Magazine, Seattle Times Pacific Magazine, USA Today, U.S. News and World Report, Health Magazine, Seattle Magazine, Self, More and others
- Several on-line news media each year
- "Preventing Breast Cancer" written commentary for ABC.com, April 2002
- Ivanhoe National TV Productions specials on Breastfeeding, Breast Cancer, and Breast Gel Study September 2002
- Reuters, "Weight loss possible with psychiatric drugs" September 2019
- Washington Post Live Saving Cancer, October 2019
- Forbes "A New Study Says Hair Dyes And Chemical Straighteners May Cause Breast Cancer December" 2019
- Medscape "Lifestyle Intervention Curbs Risk of Obesity-Related Cancers in T2D Patients in Look AHEAD" August 2020
- Gizmodo, "How Will Our Bodies Change From Being Inside for Months?" May 2020
- Yahoo, "Viral TikTok reveals pressures women face to weigh '120 pounds.' Here's why the number on the scale doesn't matter" October 2021
- U.S. Masters Swimming "How Swimming Might Prevent Cancer" February 2022
- Yahoo "'The end of dieting': How new health trackers claim to improve your health by offering insight into your body" February 2022
- Mother's Blog "Vitamin D: Does it help with weight loss?" May 2023
- MedPage Today, "Cardiorespiratory Fitness Levels May Influence Cancer Risk in Men," June 2023
- The Wall Street Journal, "Lower Your Cancer Risk with Just Four Minutes of Exercise," July 2023
- Eating Well, "What Happens to Your Body When You Eat Enough Fruits & Vegetables" December 2022

U.S. GOVERNMENT

- Testimony, on the hazards of talc, asbestos, and reports that consumer products containing these substances cause cancer, to U.S. Congress, Subcommittee on Economic and Consumer Policy, hearing on "Examining the Public Health Risks of Carcinogens in Consumer Products (https://oversight.house.gov/legislation/hearings/examining-the-public-health-risks-of-carcinogens-in-consumer-products)." March 12, 2019.

EXHIBIT B

PRIOR DEPOSITION, TRIAL AND HEARING TESTIMONY OF ANNE MCTIERNAN, MD, PhD

Deposition Testimony

1. US District Court, New Jersey, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Products Liability Litigation,* MDL No. 2738, January 28, 2019.

2. City of St. Louis, *Vickie Forrest, et al. v. Johnson & Johnson, et al.,* Cause No. 1522-CC00419-01, November 22, 2019.

3. US District Court, New Jersey, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Products Liability Litigation*, MDL No. 2738, August 19, 2021,

4. US District Court, Southern District of Florida, *In re: Zantac (Ranitidine) Products Liability Litigation,* MDL No. 2924, April 28, April 29, May 31, and October 24, 2022.

5. Chancery Court, First Judicial District of Hinds County, Mississippi, *State of Mississippi v. Johnson & Johnson,* 25CH1:14-cv-001207, October 3, 2023

6. US District Court, New Jersey, In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Products Liability Litigation, MDL No. 2738, April 2, 2024

Trial/Hearing Testimony

1. *Daubert* Hearing, US District Court, New Jersey, *In re Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Products Liability Litigation,* MDL No. 3:16-md-2738, July 25, 2019.

2. Trial Testimony, City of St. Louis, *Vickie Forrest, et al. v. Johnson & Johnson, et al.,* Cause No. 1522-CC00419-01, December 12 and 13, 2019.

3. Trial Testimony, City of St. Louis, *Victoria Giese, et al. v. Johnson & Johnson, et al.,* Cause No. 1522-CC00419-02, September 15, 2021.